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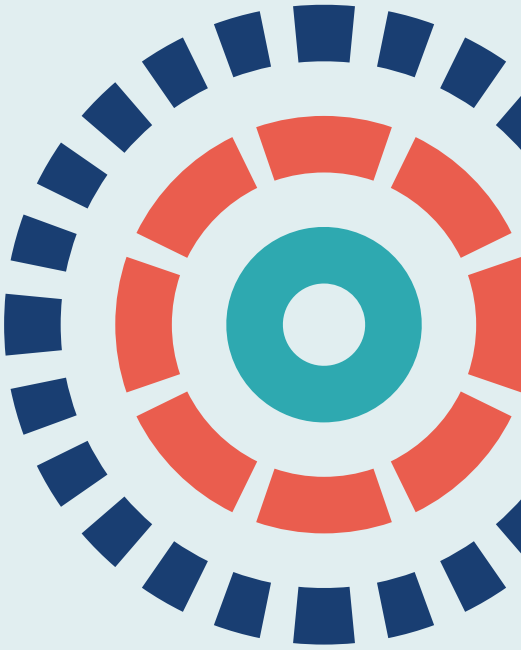

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Hannah Fraser, Daniel Gallacher, Felix Achana, Rachel Court, Sian Taylor-Phillips, Chidozie Nduka, Chris Stinton, Rebecca Willans, Paramjit Gill and Hema Mistry*

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This report

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Abstract

Rapid antigen detection and molecular tests for group A streptococcal infections for acute sore throat: systematic reviews and economic evaluation

Hannah Fraser, Daniel Gallacher, Felix Achana, Rachel Court, Sian Taylor-Phillips, Chidozie Nduka, Chris Stinton, Rebecca Willans, Paramjit Gill and Hema Mistry*

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Background: Sore throat is a common condition caused by an infection of the airway. Most cases are of a viral nature; however, a number of these infections may be caused by the group A *Streptococcus* bacterium. Most viral and bacterial sore throat infections resolve spontaneously within a few weeks. Point-of-care testing in primary care has been recognised as an emerging technology for aiding targeted antibiotic prescribing for sore throat in cases that do not spontaneously resolve.

Objective: Systematically review the evidence for 21 point-of-care tests for detecting group A *Streptococcus* bacteria and develop a de novo economic model to compare the cost-effectiveness of point-of-care tests alongside clinical scoring tools with the cost-effectiveness of clinical scoring tools alone for patients managed in primary care and hospital settings.

Data sources: Multiple electronic databases were searched from inception to March 2019. The following databases were searched in November and December 2018 and searches were updated in March 2019: MEDLINE [via OvidSP (Health First, Rockledge, FL, USA)], MEDLINE In-Process & Other Non-Indexed Citations (via OvidSP), MEDLINE Epub Ahead of Print (via OvidSP), MEDLINE Daily Update (via OvidSP), EMBASE (via OvidSP), Cochrane Database of Systematic Reviews [via Wiley Online Library (John Wiley & Sons, Inc., Hoboken, NJ, USA)], Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley Online Library), Database of Abstracts of Reviews of Effects (DARE) (via Centre for Reviews and Dissemination), Health Technology Assessment database (via the Centre for Reviews and Dissemination), Science Citation Index and Conference Proceedings [via the Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA)] and the PROSPERO International Prospective Register of Systematic Reviews (via the Centre for Reviews and Dissemination).

Review methods: Eligible studies included those of people aged ≥ 5 years presenting with sore throat symptoms, studies comparing point-of-care testing with antibiotic-prescribing decisions, studies of test accuracy and studies of cost-effectiveness. Quality assessment of eligible studies was undertaken. Meta-analysis of sensitivity and specificity was carried out for tests with sufficient data. A decision tree model estimated costs and quality-adjusted life-years from an NHS and Personal Social Services perspective.

Results: The searches identified 38 studies of clinical effectiveness and three studies of cost-effectiveness. Twenty-six full-text articles and abstracts reported on the test accuracy of point-of-care tests and/or clinical scores with biological culture as a reference standard. In the population of interest (patients with Centor/McIsaac scores of ≥ 3 points or FeverPAIN scores of ≥ 4 points), point estimates were 0.829 to 0.946 for sensitivity and 0.849 to 0.991 for specificity. There was considerable heterogeneity, even for studies using

the same point-of-care test, suggesting that is unlikely that any single study will have accurately captured a test's true performance. There is some randomised controlled trial evidence to suggest that the use of rapid antigen detection tests may help to reduce antibiotic-prescribing rates. Sensitivity and specificity estimates for each test in each age group and care setting combination were obtained using meta-analyses where appropriate. Any apparent differences in test accuracy may not be attributable to the tests, and may have been caused by known differences in the studies, latent characteristics or chance. Fourteen of the 21 tests reviewed were included in the economic modelling, and these tests were not cost-effective within the current National Institute for Health and Care Excellence's cost-effectiveness thresholds. Uncertainties in the cost-effectiveness estimates included model parameter inputs and assumptions that increase the cost of testing, and the penalty for antibiotic overprescriptions.

Limitations: No information was identified for the elderly population or pharmacy setting. It was not possible to identify which test is the most accurate owing to the paucity of evidence.

Conclusions: The systematic review and the cost-effectiveness models identified uncertainties around the adoption of point-of-care tests in primary and secondary care settings. Although sensitivity and specificity estimates are promising, we have little information to establish the most accurate point-of-care test. Further research is needed to understand the test accuracy of point-of-care tests in the proposed NHS pathway and in comparable settings and patient groups.

Study registration: The protocol of the review is registered as PROSPERO CRD42018118653.

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List of abbreviations

AMR	antimicrobial resistance
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
COBA	colistin and oxolinic acid
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
EAG	External Assessment Group
ECCMID	European Congress of Clinical Microbiology and Infectious Diseases
EQ-5D	EuroQol-5 Dimensions
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
FDA	Food and Drug Administration
FIA	fluorescent immunoassay
GP	general practitioner
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
JBI	Joanna Briggs Institute
MeSH	medical subject heading
NG	NICE Guidance
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
PCR	polymerase chain reaction
PHE	Public Health England
PPV	positive predictive value
PRISM	PRImary care Streptococcal Management
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies – 2
RADT	rapid antigen detection test
RCT	randomised controlled trial
RePEc	Research Papers in Economics
RTI	respiratory tract infection
ScHARRHUD	School of Health and Related Research Health Utilities Database
SE	standard error
STDR	sore throat decision rules
strep A	group A *Streptococcus*
strep C	group C *Streptococcus*
strep G	group G *Streptococcus*

Plain English summary

Sore throat is a common condition caused by an infection of the airway. Most cases are viral; however, a small number may be caused by the group A *Streptococcus* bacterium. Most viral and bacterial sore throat infections resolve spontaneously within a few weeks; however, some may be more serious and require antibiotics. Currently, National Institute for Health and Care Excellence guidance recommends the use of clinical scoring tools to identify patients for whom antibiotic treatment is appropriate.

Ideally, a throat swab culture should be obtained to identify the organism causing the infection in cases in which diagnosis is uncertain. However, this takes time, causing potential delays in administering the correct treatment. Point-of-care tests can be administered at or near the site of the patient; therefore, they are much faster.

Our review considered evidence for the test accuracy and cost-effectiveness of 21 point-of-care tests for detecting group A *Streptococcus* bacteria. We built an economic model, predicting costs and benefits for adults and children in a primary care or hospital setting. The findings will support the National Institute for Health and Care Excellence to make recommendations about the use of these point-of-care tests for detecting group A *Streptococcus* bacteria in the NHS in England and Wales.

The clinical effectiveness review found 38 relevant studies; of these, 26 reported on the accuracy of point-of-care tests. These studies found wide variation in the accuracy of the tests. The quality of the evidence was weak and there was little information on some of the 21 tests. As the studies were all so different, it was not possible to identify which test is the most accurate.

The economic model found considerable uncertainty about how costs and benefits would change if point-of-care tests were introduced in different care settings. Further research is needed to see whether or not point-of-care testing provides value for money.

Scientific summary

Background

Sore throat is a common condition caused by an infection of the airway. Clinical descriptions of acute sore throat include acute pharyngitis and tonsillitis, which are both infections of the upper respiratory airway affecting the mucosa. Most cases are viral; however, a small number of these infections may be caused by the group A *Streptococcus* bacterium. Most sore throats resolve spontaneously within a few weeks. An analysis of UK primary care use data identified a reduction in antibiotic prescribing in the UK between 1993 and 2001 for diagnosed episodes of sore throat. Despite this reduction, sore throat and other respiratory tract infections remain a common reason for primary care use.

Point-of-care testing (rapid antigen detection and molecular tests) in primary care has been recognised as an emerging technology for aiding targeted antibiotic prescribing in cases of sore throat. These tests are intended to be used in addition to clinical scoring systems, such as FeverPAIN and Centor. The purpose of these tests is to increase diagnostic confidence of a suspected group A streptococcal infection, to guide antimicrobial prescribing decisions in people presenting with an acute sore throat and to contribute to improving antimicrobial stewardship. The tests may be suitable for use in all settings where patients may present with an acute sore throat (Centor scores of ≥ 3 points, FeverPAIN scores of ≥ 4 points); these include primary and secondary care, and community pharmacies.

Decision question

The decision problem for this assessment is what is the clinical effectiveness and cost-effectiveness of rapid antigen detection and molecular tests in patients with high clinical scores (Centor scores of ≥ 3 points, FeverPAIN scores of ≥ 4 points), compared with the use of clinical scoring tools alone, for increasing the diagnostic confidence of suspected group A streptococcal infection in people who present with an acute sore throat in primary and secondary care?

Objectives

To systematically review the evidence for the clinical effectiveness of rapid antigen detection and molecular tests; systematically review existing economic evaluations; and develop a de novo economic model to assess the cost-effectiveness of rapid antigen detection and molecular tests in conjunction with clinical scoring tools compared with clinical scoring tools alone in England and Wales.

Methods

Clinical effectiveness and cost-effectiveness systematic reviews

Multiple electronic databases were searched from inception to March 2019 for both the clinical effectiveness reviews and the cost-effectiveness reviews.

The following databases were searched in November and December 2018 and searches were updated in March 2019: MEDLINE [via OvidSP (Health First, Rockledge, FL, USA)], MEDLINE In-Process & Other Non-Indexed Citations (via OvidSP), MEDLINE Epub Ahead of Print (via OvidSP), MEDLINE Daily Update (via OvidSP), EMBASE (via OvidSP), Cochrane Database of Systematic Reviews [via Wiley Online Library (John Wiley & Sons, Inc., Hoboken, NJ, USA)], Cochrane Central Register of Controlled

Trials (CENTRAL) (via Wiley Online Library), Database of Abstracts of Reviews of Effects (DARE) (via the Centre for Reviews and Dissemination), Health Technology Assessment database (via the Centre for Reviews and Dissemination), Science Citation Index and Conference Proceedings [via the Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA)] and the PROSPERO International Prospective Register of Systematic Reviews (via the Centre for Reviews and Dissemination).

Supplementary searches were used to identify additional published and unpublished studies. Reference lists of the included studies and information provided by the manufacturers of the intervention tests were checked for additional eligible studies.

Two reviewers independently screened and assessed titles and abstracts of all records. Studies were included according to the following criteria:

- Population – people aged ≥ 5 years presenting with symptoms of an acute sore throat.
- Intervention – point-of-care tests for group A *Streptococcus* (including rapid antigen detection tests and molecular tests), preferably in those identified as being at high risk.
- Comparator – antibiotic-prescribing decisions using clinical scoring tools for group A *Streptococcus*, such as FeverPAIN or Centor/modified Centor (McIsaac) alone.
- Reference standard – microbiological culture.
- Outcomes – any patient-related outcome, test accuracy (the ability of a test to correctly differentiate between people who do and people who do not have a disease) or performance, prescribing behaviour and cost-effectiveness estimates.
- Study design – clinical test accuracy studies that compare the index tests and/or FeverPAIN/Centor/McIsaac scores with throat swab culture. Studies of head-to-head comparisons of rapid tests were eligible for inclusion if test accuracy statistics were reported for each test. For prescribing behaviour, any study design that compared the index test and/or clinical scores (i.e. FeverPAIN/Centor/McIsaac) with culture was eligible. For cost-effectiveness, any full economic evaluations (or economic models) reporting both cost and outcome estimates were eligible.
- Health-care setting – primary care (general practice clinics, community pharmacies and walk-in centres) and secondary care (urgent care/walk-in centres and emergency departments) settings.

Data were extracted by one reviewer and checked by a second reviewer. Discrepancies were resolved via discussion or by a third reviewer. Evidence was synthesised using narrative review and statistical methods where appropriate. Meta-analyses were undertaken in Stata® version 15 (StataCorp LP, College Station, TX, USA).

Study quality assessment of eligible studies was undertaken using recognised checklists [tailored Quality Assessment of Diagnostic Accuracy Studies – 2 (QUADAS-2), Cochrane Risk of Bias, Joanna Briggs Institute Critical Appraisal Checklist for analytical cross-sectional studies and Consolidated Health Economic Evaluation Reporting Standards (CHEERS)].

Cost-effectiveness model

A de novo decision tree model was built in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) to assess the cost-effectiveness of rapid antigen detection and molecular tests in conjunction with clinical scoring tools, compared with the use of clinical scoring tools alone. The base-case economic model included adult patients who were seen in primary care with suspected group A streptococcal infection. The base-case model was adapted to look at the following subgroups with suspected group A streptococcal infection: adult patients seen in the hospital, children seen in primary care and children seen in the hospital. The data for the model included prevalence information from the systematic clinical effectiveness review, published literature and expert opinion. The model estimated the mean total costs and mean total quality-adjusted life-years for each rapid antigen detection test and molecular test over a 1-year time horizon, and adopted an NHS and Personal Social Services perspective. Costs were in 2017/18 prices. No discounting of costs and outcomes was undertaken. Outcomes are reported as incremental cost-effectiveness ratios expressed in terms of

cost per quality-adjusted life-year gained. A number of sensitivity analyses were undertaken. Probability sensitivity analyses were also undertaken (1000 model runs).

Results

The searches identified 5919 records of clinical effectiveness and 6980 records of cost-effectiveness, of which we included 38 and three studies, respectively.

The systematic review of clinical effectiveness studies identified 38 studies that used the point-of-care tests identified in the National Institute for Health and Care Excellence scope and/or clinical scores with biological cultures as a reference standard. These comprised 26 full-text articles, three abstracts, five manufacturer's submissions (submitted directly to the National Institute for Health and Care Excellence in response to a request for information) and four US Food and Drug Administration documents. There were 26 studies (23 full-text articles and three abstracts) that reported test accuracy data. The methodological quality of the included studies was poor. In particular, in 65.4% (17/26) of studies it was unclear whether the sample was consecutive or convenience. Convenience samples may not provide a true representation of the prevalence of group A streptococci. There was judged to be a high level of bias concerning methods of patient selection. Overall, the findings reveal variations in the sensitivity (0.679 to 1.00) and specificity (0.733 to 1.00) estimates of point-of-care tests. These point estimates were 0.829 to 0.946 for sensitivity and 0.849 to 0.991 for specificity in high-risk populations, including patients with Centor/McIsaac scores of > 2 points, representing the population of interest. These estimates do not account for any of the unpublished manufacturer submissions.

Direct comparison with sore throat clinical scoring tools revealed that point-of-care tests were generally more specific. However, one methodological limitation concerns the varying way that clinical scoring tools have been implemented across the included studies. For instance, different studies apply different clinical score cut-off points when recruiting patients. None of these studies matched the proposed pathway of care and treatment for patients with acute streptococcal pharyngitis, which would entail evaluating the test accuracy of a combined strategy of sore throat clinical scores at the recommended National Institute for Health and Care Excellence thresholds (Centor/McIsaac score of ≥ 3 points or FeverPAIN score of ≥ 4 points) and point-of-care tests. This limitation potentially holds important economic implications, as attempts to model this proposed pathway may not be informed by the availability of empirical data. In addition, the over-representation of the Alere™ TestPack +Plus (Abbott Laboratories, Abbott Park, IL, USA) group A streptococcal test relative to other point-of-care tests, as well as the overlap of patients across different age groups, potentially raises applicability concerns in the economic model.

Data for test accuracy were sparse for each combination of test, population and setting. There were very few head-to-head (direct) comparison studies between index tests. It was not possible to identify which test is the most accurate owing to the lack of available evidence. There was a large degree of heterogeneity among results for studies using the same rapid test. Where a test is reported in several studies, its accuracy may appear lower than that of tests reported in only a single study, particularly those at high risk of bias or with unpublished methods, so we report on number and quality of data available as well as accuracy estimates. The heterogeneity introduced by the differing characteristics of the studies further confounded attempts to produce meaningful estimates of test performance, such as care setting, age group, throat score restriction and disease prevalence. Owing to the potential heterogeneity, estimates for the sensitivity and specificity of each test were stratified by age group, throat score and care setting, although a lack of evidence meant that generalisations had to be made for the majority of estimates.

Of the scoped secondary outcomes, our search identified only studies discussing antibiotic-prescribing rates and appropriateness ($n = 12$). There is some randomised controlled trial evidence to suggest

that the use of rapid antigen detection tests may help to reduce antibiotic-prescribing rates, but there was no evidence on the effect of using molecular technologies. If a test was proven to be extremely accurate, then it is plausible that clinical staff would trust the outcomes. No information was found on the number of appointments required per episode, morbidity, mortality, onward transmission of infection, health-related quality of life, patient satisfaction with the test or health-care professional satisfaction with the test.

Cost-effectiveness

The systematic review of cost-effectiveness studies identified three studies that used the rapid antigen detection tests, as identified in the National Institute for Health and Care Excellence scope, and were classed as economic evaluations. Two studies had some notable limitations and data could not be fully extracted. The one study that allowed a full data extraction was classed as a high-quality economic evaluation when checked against the CHEERS reporting tool.

Fourteen of the 21 tests listed in the National Institute for Health and Care Excellence's scope had data on test accuracy and costs that were relevant to be included in the final economic modelling. In the base-case analysis, which included adult patients seen in primary care with suspected group A streptococcal infection, the economic model found considerable uncertainty about the cost-effectiveness of the different point-of-care tests for suspected group A streptococcal infection. This finding was also seen in the other economic models that were adapted (adult patients seen in the hospital, children seen in primary care and children seen in the hospital). Important uncertainties in the model include parameter inputs and assumptions that increase the (1) cost of testing (acquisition cost of test, additional clinician time for administering and processing test results, and cost of confirmatory throat culture for those testing negative) and (2) penalty for antibiotic overprescription/unnecessary antibiotic use (acquisition cost of antibiotic and probabilities for penicillin-induced anaphylaxis and rash).

Discussion and conclusions

Main findings

The systematic review and cost-effectiveness model identify uncertainties around the adoption of point-of-care tests in the NHS. The available evidence is heterogeneous in populations studied, design, methods and analysis. Although sensitivity and specificity estimates are promising, we have little information on the best point-of-care test to use. Although there is potential for the point-of-care tests to be cost-effectiveness in both primary and secondary care settings, key parameter inputs and modelling assumptions need to be confirmed and model findings remain uncertain.

Strengths and limitations

Strengths of the work include a robust and comprehensive systematic review strategy (literature search, data extraction and analysis) and the building of a de novo decision tree model to assess cost-effectiveness.

No studies on point-of-care use in a pharmacy setting or in the elderly population were retrieved. In addition, no study matched the proposed pathway of care and treatment for patients with acute streptococcal pharyngitis, which would entail evaluating the test accuracy of a combined strategy of sore throat clinical scores at the recommended National Institute for Health and Care Excellence thresholds (i.e. Centor/McIsaac score of ≥ 3 points or FeverPAIN score of ≥ 4 points) and point-of-care tests in the age groups defined in the scope.

Although the economic model represented the clinical care pathway in the NHS, practice and management will vary from site to site (within and across both primary care settings and secondary care settings). The modelling may have underestimated the costs as we did not take into account the different strains of group A *Streptococcus*, which may have influenced test performance and altered the

profile of complications, seasonality of group A streptococcal infection and the onward transmission of the infection.

Implications for health care

Our findings indicate that point-of-care testing was not cost-effective within the current thresholds and should be viewed cautiously by clinicians and policy-makers, in view of the poor quality of the evidence that was available to us. Health-care professionals should be mindful of the potential variation in performance of the different testing methods and strategies in their day-to-day practice.

Research priorities

Further research is needed to understand the test accuracy of point-of-care tests within the proposed NHS pathway and within comparable settings and patient groups. Future work that considers head-to-head test accuracy studies or randomised controlled trials using multiple point-of-care tests in relevant populations would provide relevant comparator information and determine the value of point-of-care testing.

Study registration

The protocol of the review is registered as PROSPERO CRD42018118653.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 31. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Description of the health problem

Sore throat is a common condition;[1,2] clinical descriptions of acute sore throat include acute pharyngitis and tonsillitis, which are both infections of the upper respiratory airway affecting the mucosa.[3,4] In a Scottish survey, 31% of respondents reported having experienced a severe sore throat in the previous 12 months.[1] Symptoms of sore throat include pain in the throat and may also include fever or headache; however, not all patients will require or seek medical advice and/or treatment for these symptoms. An analysis of UK primary care use data identified a reduction of diagnosed episodes of sore throat in the UK between 1993 and 2001.[2] This finding may suggest changes in patient behaviour regarding self-care, changes in general practitioner (GP) diagnosis and recording of sore throat or an actual change in the prevalence of sore throat, although there is no evidence to support these theories. Despite this reduction, sore throat and other respiratory tract infections (RTIs) remain a common reason for primary care use; one-quarter of the population will visit their GP because of a RTI each year.[5]

In the UK, diagnosis of sore throat is currently based mainly on clinical assessment and it is recommended by the National Institute for Health and Care Excellence (NICE) that the FeverPAIN[6] or Centor[7] criteria are also used. The FeverPAIN and Centor tools were designed to predict group A *Streptococcus* (strep A) (Centor, FeverPAIN), group C *Streptococcus* (strep C) (FeverPAIN) and group G *Streptococcus* (strep G) (FeverPAIN),[6,7] and have been proposed as methods by which clinicians can identify which patients are most likely to benefit from antibiotic use for sore throat.[8] This is because sore throat is often a self-limiting illness; most cases have a viral aetiology and, therefore, antibiotics would not be an effective treatment in these instances. In addition, as antibiotics reduce the duration of symptoms by only a very short period, this must be traded off against the side effects. Around 5–17% of sore throats are due to a bacterial infection, typically group A beta-haemolytic *Streptococcus*, also known as '*Streptococcus pyogenes*', 'group A *Streptococcus*', 'GAS' or 'strep A'.[5,8] Expert advice suggests that bacterial sore throat can also be caused by group C and group G streptococci; however, strep A is thought to account for around 80% of bacterial throat infections, and groups C and G streptococci are thought to account for around 20%. Most cases of strep A infection resolve without complications and, in fact, many people carry the bacterium without experiencing illness. Despite these factors, most patients presenting with sore throat in the UK will be given antibiotics in primary care.[9,10] Although rates of antibiotic prescribing for sore throat declined between 1993 and 2001, more recent prescribing data, for 2011, remain close to the 2001 figure, with median practice-prescribed antibiotics for sore throat at 60%.[8] RTIs, which include sore throats, account for a large proportion of antibiotic use in general practice in the UK (approximately 60%).[8]

There are clinical and epidemiological reasons why clinicians may prescribe antibiotics for sore throat in the absence of microbiological confirmation. The first is practical. The current reference standard, culture of the bacteria grown from a throat swab, takes > 18 hours for a result to be obtained.[11] Where clinicians suspect strep A infection based on clinical judgement and use of the FeverPAIN or Centor criteria, there is an opportunity to reduce the risk or harm caused by complications such as tonsillitis, pharyngitis, scarlet fever, impetigo, erysipelas (an infection in the upper layer of the skin), glomerular nephritis, rheumatic fever, cellulitis and pneumonia. Some vulnerable patient groups, such as those who are immunocompromised, are at a higher risk of developing invasive strep A infection. To prevent onward transmission, current Public Health England (PHE) guidance on invasive strep A infection management[12] indicates use of antibiotics in close contacts of people who have invasive strep A infection if they have symptoms of strep A infection, such as sore throat, themselves or are in a particular risk group or setting.[11] Although these factors must be considered in understanding the

reasons for use of antibiotics to treat sore throat in the absence of more accurate diagnosis, another factor that has an impact on use is patient demand. Although patient attendances for minor ailments at GP surgeries have reduced, when patients do visit their GP there is an expectation of intervention, and this is increasingly the case.[11] Furthermore, RTIs account for a high proportion of working days lost in the UK – in 2016, almost one-quarter (24.8%, 34 million days) – so ensuring that patients receive appropriate and timely treatment also has an economic impact on the UK economy and on patients.[13] However, this rationale and the demands need to be balanced with the aforementioned statistics regarding the low prevalence of bacterial infection in sore throat and the risk of antimicrobial resistance (AMR).

Overuse or inappropriate use of antibiotics can lead to bacteria developing resistance, leading to an emergence of multidrug-resistant pathogens, which are increasingly difficult to treat. AMR could contribute to an estimated 10 million deaths every year globally by 2050 and a global productivity cost of £66T.[11] In response to this threat, 'antimicrobial stewardship' has been a central strategy adopted by the Chief Medical Officer and NICE.[11,14] Point-of-care testing in primary care has been recognised as an emerging technology for aiding targeted antibiotic prescribing in cases of sore throat, by supporting clinicians with diagnosis and communicating appropriate use of antibiotics to patients.[15] Several technologies have been developed for point-of-care testing in primary care for appropriate administration of antibiotics to those who would benefit and to prevent delay and associated complications.

The NICE Diagnostics Advisory Committee is tasked with providing guidance to the NHS about the use of point-of-care tests for the detection of strep A in sore throat infections. To inform the Diagnostics Advisory Committee, the External Assessment Group (EAG) has provided this assessment of the clinical accuracy and cost-effectiveness of point-of-care tests for the detection of strep A as a replacement or adjunct for standard assessment procedures. The potential value of the point-of-care tests is in rapidly determining the presence and nature of a bacterial infection.

Aetiology and pathology

Most sore throats are caused by an infection, mainly viral, and so are typically spread from person to person via respiratory droplets; non-infectious causes are uncommon.[3] In the case of infectious causes, viruses, bacteria or fungi invade the upper respiratory mucosa, causing a local inflammatory response.[4] Complications associated with sore throat caused by infection are rare; however, strep A infection has a small risk of the following complications:[3]

- otitis media
- acute sinusitis
- peritonsillar abscess
- rheumatic fever and post-streptococcal glomerulonephritis are also complications associated with strep A throat infection; however, these are extremely rare in developed countries
- invasive strep A, if the bacteria move from the throat into a sterile body site (which can lead to severe infections, sepsis and streptococcal toxic shock syndrome).

Children are most likely to carry or be infected by strep A; however, people aged > 65 years or those whose immune system is compromised (e.g. people living with a human immunodeficiency virus infection, diabetes mellitus, heart disease or cancer and people using high-dose steroids or intravenous drugs) are at higher risk of developing an invasive strep A infection.[16]

A *Fusobacterium necrophorum* infection affecting the pharynx or tonsils can (very rarely) lead to Lemierre's syndrome (sepsis and jugular vein thrombosis).[3]

Diagnosis and care pathway

Figure 1 depicts the care pathway for assessing and treating a sore throat as outlined in the NICE antimicrobial prescribing guidance on sore throat [NICE Guidance (NG) number 84 (NG84)].[8] Most uncomplicated sore throats are managed without seeking medical advice and tend to resolve within 1 week.[10] Suggested conservative measures include simple analgesia, maintaining hydration, salt gargling and throat lozenges. In selected cases in which a GP, or a pharmacist or a health-care practitioner in the secondary care setting, such as in accident and emergency, feels that the patient may benefit from antibiotics, the prescriber should apply either the FeverPAIN or the Centor scores to guide their decision-making. The NICE antimicrobial prescribing guideline on acute sore throat does not make any recommendations about using point-of-care tests or throat cultures to confirm strep A infection.[8]

Significance to the NHS and current service cost

The significance of sore throat and inappropriate use of antibiotics to the NHS broadly falls into two categories: the first is associated with health-care use directly owing to sore throat and the second is the impact of inappropriate use of antibiotics contributing to AMR.

Respiratory tract infections, including sore throat, account for a large proportion of primary care use and antibiotic prescribing.[10] However, there is already evidence that the majority of patients prefer to self-medicate minor ailments, such as sore throat, where they feel able to do so.[1,2,14] For example, a visit to the general practice for a diagnosis and treatment for sore throat incurs the cost of the visit to a general practice and any treatment prescribed. In addition, in the current system, in which GPs can use the FeverPAIN or Centor criteria to inform antibiotic prescribing, there is the potential cost of additional health-care use for patients whose condition does not improve or who develop complications owing to ineffective or no treatment being prescribed. The risk of complications, however, is low and current prescribing activity suggests overuse rather than underuse of antibiotics for sore throat. Another cost associated with the current system is laboratory costs where the reference standard for diagnosis is used, namely throat swabs sent for culture.

Although these costs and the impact of minor ailment use on the NHS is a key consideration, the primary aim of the intervention being considered is to reduce inappropriate antibiotic prescribing. Doing so could support a reduction in promoters of AMR. The main antibiotic prescribed by general practice is penicillin, and this is the first-line treatment currently recommended by NICE for suspected strep A throat infection.[8,15] Across Europe, an estimated 25,000 people die each year as a result of hospital infections caused by the five

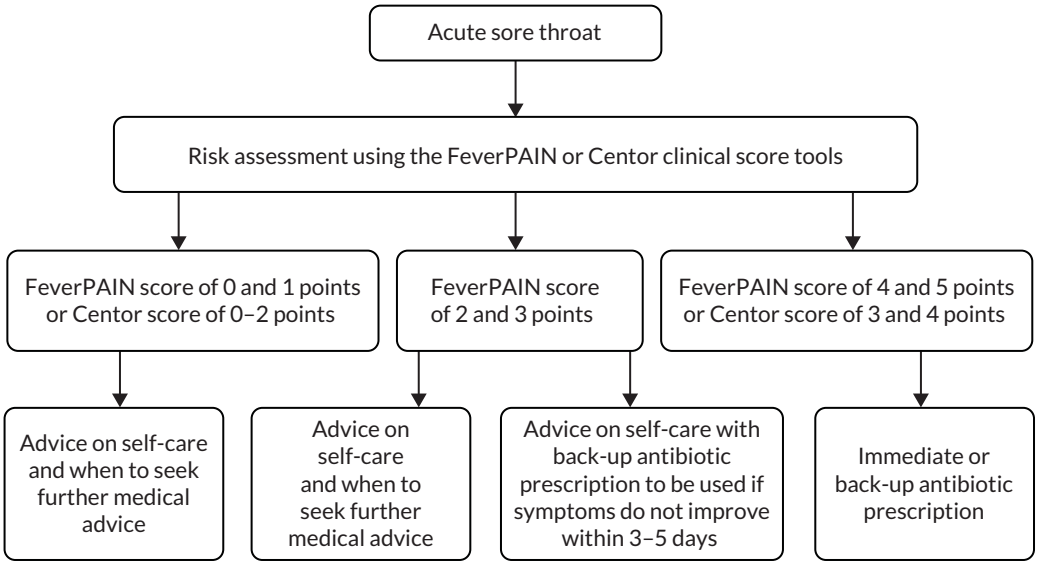

FIGURE 1 Diagnostic and care pathway for managing acute sore throat in patients who are not at high risk of complications.

most common resistant bacteria, and a parliamentary report estimated the annual cost to the NHS to be £180M per year.[17] Although it is often possible at present to use alternative treatments to treat resistant infection, costs of treatment and risk of mortality for a resistant infection are likely to be approximately double the cost of a non-resistant infection.[17] One study investigating the cost of a 10-month outbreak of a type of antibiotic-resistant bacteria (carbapenemase-producing enterobacteria) found the total cost to be close to £1M. The main cost was missed revenue from cancellation of planned surgical procedures owing to ward closures and lack of bed space. Other costs were associated with additional staff time, increased length of patient stay in hospital, screening, bed and ward closure, contact precautions, anti-infective costs, human papillomavirus decontamination and ward-based monitors.[17] In addition to health-care costs and risk of litigation associated with AMR-related harm, there is a wider societal cost of lost productivity and reduced quality of life for patients suffering the effects of AMR infections.

Clear definition of interventions

There are rapid tests for the strep A bacterium, which are intended to be used in addition to clinical scoring systems, such as FeverPAIN and Centor. The purpose is to increase diagnostic confidence in a suspected strep A infection, to guide antimicrobial prescribing decisions in people presenting with an acute sore throat and to contribute to improving antimicrobial stewardship. The tests may be suitable for use in all settings where patients may present with an acute sore throat; these include both primary and secondary care, and community pharmacies.[11]

Twenty-one rapid tests for strep A detection are available. The tests use either immunoassay detection methods [rapid antigen detection tests (RADTs)] or molecular methods [polymerase chain reaction (PCR) or isothermal nucleic acid amplification]. The tests listed in the following section were identified from the NICE scope on point-of-care testing in primary care for strep A infection in sore throat.

Comparative technical overview of the point-of-care tests for group A *Streptococcus*

Seventeen RADTs were identified, and their product properties are summarised in *Table 1*. The type of information provided by each of the manufacturers is summarised in *Appendix 14*. For each test, the limit of detection has been defined as the lowest concentration of strep A in a sample that can be distinguished from negative samples. Of these, 16 tests use lateral flow techniques (also known as immunochromatographic or immunofluorescent assays) and one test is a turbidimetric immunoassay.

Four molecular tests were identified which use nucleic acid amplification techniques, either PCR or isothermal nucleic acid amplification, to amplify and detect a specific fragment of the GAS genome (*Table 2*). In each test, any strep A deoxyribonucleic acid present in the sample is labelled during the reaction, producing fluorescent light, which is monitored by a reader. If fluorescence reaches a specific threshold, the test is considered positive. If the threshold is not reached during the set time (usually up to 15 minutes), the test is negative.

The lateral flow (immunochromatographic and immunofluorescence) tests require a throat swab, which is typically placed into a specimen extraction tube and mixed with reagents to extract the sample from the swab. The swab is discarded and then either a test strip is immersed in the extracted solution or drops of the extracted solution are added to the sample well of a test cassette. The sample then migrates along the test strip or cassette, with any strep A antigens present in the sample binding to immobilised strep A antibodies in the test strip or cassette. When strep A is present at levels above the detection limit of the test, a line appears in the test line region of the strip or cassette. A control line shows technical success of the test. Results should be discarded when the control line indicates that the test

TABLE 1 Rapid antigen detection tests: product descriptions and properties from manufacturers' data

Product	Test format and supply	Method	Limit of detection	Description of results	Time to result (minutes)[a]
Clearview® Exact Strep A cassette[b] (Abbott Laboratories, Lake Bluff, IL, USA)	25 individually pouched test cassettes	Lateral flow (immunochromatography)	5×10^4 organisms/test	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
Clearview Exact Strep A dipstick – test[b] strip (Abbott Laboratories, Lake Bluff, IL, USA)	25 test kits Dipstick	Lateral flow (immunochromatography)	5×10^4 organisms/test	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
BD Veritor Plus system group A strep assay – cassette (Becton Dickinson and Company, Sparks, MD, USA)	30 test kits Test cassette	Lateral flow (immunochromatography)	Strain 12384: 1×10^5 CFU/ml Strain 19615: 5×10^4 CFU/ml Strain 25663: 2×10^5 CFU/ml	Analysed by a BD Veritor system analyser module. Results are displayed visually	5
Strep A Rapid Test – cassette (Biopanda Reagents, Belfast, UK)	20 test cassettes	Lateral flow (immunochromatography)	1×10^5 organisms/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
Strep A Rapid Test – test strip (Biopanda Reagents, Belfast, UK)	No information provided	Lateral flow (immunochromatography)	1×10^5 organisms/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
NADAL® Strep A – test strip (nal von minden GmbH, Regensburg, Germany)	40 test strips including controls, 50 test strips (tube) including controls, as well as positive and negative control vials	Lateral flow (immunochromatography)	1.5×10^5 organisms/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5

continued

TABLE 1 Rapid antigen detection tests: product descriptions and properties from manufacturers' data (*continued*)

Product	Test format and supply	Method	Limit of detection	Description of results	Time to result (minutes)[a]
NADAL Strep A – cassette (nal von minden GmbH, Regensburg, Germany)	20 test cassettes including controls as well as positive and negative control vials	Lateral flow (immunochromatography)	1.5×10^5 organisms/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
NADAL Strep A plus – cassette (nal von minden GmbH, Regensburg, Germany)	20-pack cassettes including controls and five-pack cassettes including controls	Lateral flow (immunochromatography)	1.5×10^5 organisms/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
NADAL Strep A plus – test strip (nal von minden GmbH, Regensburg, Germany)	40 test strips	Lateral flow (immunochromatography)	1.5×10^5 organisms/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
NADAL Strep A scan test – cassette (nal von minden GmbH, Regensburg, Germany)	20-pack cassettes including controls	Lateral flow (immunochromatography)	1.5×10^5 organisms/swab	Extracted solution is placed into the test cassette, with the Colibri placed on top. Analysed using a Colibri reader and Colibri USB and software (nal von minden GmbH, Regensburg, Germany)	5
OSOM Strep A test – test strip (Sekisui Diagnostics, Burlington, MA, USA)	50-test pack	Lateral flow (immunochromatography)	Not known	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
QuikRead Go Strep A test kit (Orion Diagnostica, Espoo, Finland)	50 tests including controls	Turbidimetric immunoassay	7×10^4 CFU/swab	Analysed using the QuikRead Go instrument	< 7[a]
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories, Lake Bluff, IL, USA)	20 or 40 tests	Lateral flow (immunochromatography)	Not known	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5

Product	Test format and supply	Method	Limit of detection	Description of results	Time to result (minutes)[a]
bioNexia® Strep A plus – cassette (bioMérieux, Marcy-l'Étoile, France)	25 test cassettes	Lateral flow (immunochromatography)	1×10^4 organisms/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
bioNexia Strep A dipstick – test strip (bioMérieux, Marcy-l'Étoile, France)	25 test strips	Lateral flow (immunochromatography)	Not known	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
Biosynex Strep A – cassette (Biosynex, Illkirch-Graffenstaden, France)	Not reported	Lateral flow (immunochromatography)	1×10^5 bacteria/swab	Positive results are indicated by two lines: one in the control region and the other in the test region. Read by visual inspection	5
Sofia Strep A FIA (Quidel, San Diego, CA, USA)	25 cassettes, including positive and negative control vials	Lateral flow (immunofluorescence)	Strain Bruno [CIP 104226]: 1.86×10^4 CFU/test Strain CDC-SS-1402: 9.24×10^3 CFU/test Strain CDC-SS-1460: 2.34×10^4 CFU/test	Analysed using the Sofia analyser, which interprets the immunofluorescent signal using on-board method-specific algorithms. Results are displayed on screen as positive, negative or invalid	5–6

CFU, colony-forming unit; CIP, ciprofloxacin; DNA, deoxyribonucleic acid; FIA, fluorescent immunoassay; USB, Universal Serial Bus.
a This information was obtained from NICE's MedTech Innovation Briefing 145.[16]
b Clearview Exact Strep A cassette and Clearview Exact Strep A dipstick – test strip (both from Abbott Laboratories) have been updated and replaced with the Clearview Exact 2.

TABLE 2 Molecular tests: product descriptions and properties

Product	Test supply and format	Method	Analyser	Limit of detection	Description of results	Time to result (minutes)[a]
Alere i Strep A (Abbott Laboratories, Lake Bluff, IL, USA)	24 test kits	Isothermal nucleic acid amplification	Alere i instrument	Strain: • ATCC 12344: 4.2 CFU/ml • ATCC 19615: 41.8 CFU/ml	Alere i instrument heats, mixes and detects, then presents results automatically on the digital display	< 8
Alere i Strep A 2 (ID NOW™ Strep A 2)[b] (Abbott Laboratories, Lake Bluff, IL, USA)	Information not available	Isothermal nucleic acid amplification	Alere i instrument	Not provided by manufacturer	Alere i instrument heats, mixes and detects, then presents results automatically on the digital display	< 6
cobas® Strep A Assay (Roche Diagnostics, Basel, Switzerland)	Strep A assay box of 20	PCR	cobas Liat® analyser (Roche Diagnostics, Basel, Switzerland)	Strain: • ATCC BAA-946: 5 CFU/ml • ATCC BAA-1066: 10 CFU/ml • ATCC 12370: 10 CFU/ml • ATCC 700294: 20 CFU/ml	Results displayed digitally	< 15
Xpert® Xpress Strep A (Cepheid, Sunnyvale, CA, USA)	Each kit contains sufficient reagents to process 10 specimens or quality control samples	PCR	GeneXpert® system (Cepheid, Sunnyvale, CA, USA)	Strain: • ATCC BAA-946 • ATCC 19615 • 9–18 CFU/ml in a transport medium or 3–6 CFU/test	Results displayed digitally	≥ 18

CFU, colony-forming unit; DNA, deoxyribonucleic acid.
a This information was obtained from NICE's MedTech Innovation Briefing 145.[16]
b The Alere i and Alere i Strep A 2 have now been replaced with the ID NOW Strep A 2.

has failed (i.e. no line appears in the control line region). Depending on the technology, the results are read either by visual inspection or by using an automated test reader device.

The turbidimetric immunoassay has similar sample collection and extraction steps to the lateral flow tests, but the extracted solution is placed into a cuvette that is prefilled with reagents. This contains rabbit anti-strep A antibodies, which bind to strep A antigens present in the sample. The QuikRead Go (Orion Diagnostica, Espoo, Finland) instrument measures the absorbance of each cuvette and converts the absorbance value into a positive or negative result.

Several of the companies recommend that negative RADT results are confirmed by microbiological culture of a throat swab.

Target population

The population of interest is people aged ≥ 5 years presenting to health-care providers in a primary care (GP surgeries and walk-in centres), secondary care (urgent care/walk-in centres and emergency departments) or community pharmacy setting with symptoms of an acute sore throat. These patients are identified as being more likely (FeverPAIN score of 2 or 3 points) or most likely (FeverPAIN score of 4 or 5 points, or a Centor score of 3 or 4 points) to benefit from an antibiotic by a clinical scoring tool. Relevant subgroups to be evaluated may include children (aged 5–14 years), adults (aged 15–75 years) and the elderly (adults aged > 75 years). In elderly patients, the infection is more likely to be invasive and have a higher associated mortality rate.

Comparator

The comparator is antibiotic prescribing based on clinical judgement and clinical scoring tools alone for strep A. However, the literature search for the comparator arm may also result in evidence referring to clinical scoring for group C and group G streptococci. The clinical scoring tools that may be used in NHS practice are FeverPAIN and Centor/modified Centor (McIsaac). These criteria are based on research evidence that assessed the individual and combination of sore throat symptoms most likely to be present in patients with clinically confirmed streptococcal infection (whether strep A or non-strep A).

FeverPAIN

The FeverPAIN clinical scoring tool includes the following variables:

- clinical history
  - sore throat (none, mild, moderate or severe)
  - cough or cold symptoms (none, mild, moderate or severe)
  - muscle aches (none, mild, moderate or severe)
  - fever in last 24 hours (yes or no)
  - onset of illness (0–3, 4–7 or > 7 days)
- clinical examination
  - cervical glands (none, 1–2 or > 2 cm)
  - inflamed tonsils (none, mild, moderate or severe)
  - pus on tonsils (yes or no).

The result of FeverPAIN is presented as a score ranging from 0 to 5 points, with 1 point assigned for each symptom present.

Centor

The Centor clinical scoring tool includes the following variables:

- cough (yes or no)
- exudate or swelling on tonsils (yes or no)
- tender/swollen anterior cervical lymph nodes (yes or no)
- temperature > 38 °C (yes or no).

Expert advice suggests that the McIsaac (modified Centor) clinical scoring tool may also be used. The McIsaac score adjusts the Centor score to account for the higher incidence of strep A in children and the reduced incidence of strep A in older adults. This adds age criteria (3–14 years, 15–44 years and ≥ 45 years) and adds 1 point for those aged < 15 years and subtracts 1 point for those aged > 45 years. The Centor result is presented as a score ranging from 0 to 4 points (0–5 points for the modified Centor), with 1 point assigned for each symptom present.[18]

Reference standard

The reference standard for assessing the test accuracy of point-of-care tests for strep A infections is microbiological culture of throat swabs using standard blood agar or streptococcal selective agar as the culture medium. In the latter, antibiotics can be added to the standard blood agar to suppress the normal pharyngeal microflora, thus improving the yield of the strep A bacteria. However, there is no consensus on the preferred medium.[19]

Throat swab culture remains the best reference standard for diagnosing streptococcal pharyngitis. However, several studies have identified discordance between throat swab culture with PCR or other measures.[20–22]

In recent studies, PCR techniques were used as arbitrators of discordant results between throat culture and point-of-care tests.[20,23,24] In point-of-care tests, a threshold quantity of viable organisms must be exceeded for culture to be positive, whereas PCR-based tests are able to detect the genome of organisms irrespective of their viability. However, PCR cannot distinguish between acute strep A pharyngitis and asymptomatic pharyngeal carriage and, therefore, may detect carriage in the absence of a streptococcal infection. Therefore, our reference standard does not include PCR. Furthermore, some of the index tests are PCR based, and so a PCR-based reference standard would be biased in favour of these index tests. Where such arbitration using PCR is reported, we have included these data in this report, but the main analysis uses culture as the reference standard.

Chapter 2 Definition of the decision problem

Decision question

This report undertaken for the NICE Diagnostics Assessment Programme examines the clinical effectiveness and cost-effectiveness of point-of-care tests for diagnosing group A streptococcal infections in people who present with an acute sore throat in primary care, secondary care or community pharmacy settings. The report will help NICE to make recommendations about how well the tests work and whether or not the benefits are worth the cost of the tests, when used in the NHS in England and Wales. The assessment also considers other outcomes, including antibiotic prescription behaviour, clinical improvement in patients' symptoms and costs associated with treatment, based on evidence identified through systematic literature searches.

The decision question for this project is what is the clinical effectiveness and cost-effectiveness of rapid antigen detection and molecular tests in patients with high clinical scores (i.e. Centor scores of ≥ 3 points, FeverPAIN scores of ≥ 4 points), compared with the use of clinical scoring tools alone, for increasing the diagnostic confidence of suspected group A streptococcal infection in people who present with an acute sore throat in primary, secondary or pharmacy care?

Overall aim of the assessment

The overall aim of this report was to present evidence on the clinical effectiveness and cost-effectiveness of rapid antigen detection and molecular tests in those with high clinical scores (i.e. Centor scores of ≥ 3 points, FeverPAIN scores of ≥ 4 points), compared with the use of clinical scoring tools alone, for increasing the diagnostic confidence of suspected group A streptococcal infection in people aged ≥ 5 years who present with an acute sore throat in primary, secondary or pharmacy care.

Objectives

- To systematically review the evidence for the clinical effectiveness of selected rapid tests for group A streptococcal infections in people aged ≥ 5 years with a sore throat presenting in a primary, secondary or pharmacy setting.
- To systematically review existing economic evaluations and develop a de novo economic model to assess the cost-effectiveness of rapid tests in conjunction with clinical scoring tools for group A streptococcal infections compared with clinical scoring tools alone.

Chapter 3 Clinical effectiveness review

Methods

Search strategies for clinical effectiveness

The search strategy for the clinical effectiveness review is detailed in *Appendix 1*. An iterative procedure was used to develop the database search strategies, building on the scoping searches undertaken by NICE for this assessment and the searches underpinning the related MedTech innovation briefing published by NICE in 2018.[16] Database searches were run in November and December 2018 and were updated in March 2019. No date or language limits were applied. Grey literature searches were undertaken in February and March 2019.

Briefly, the search strategy included:

- databases – MEDLINE [via OvidSP (Health First, Rockledge, FL, USA)], MEDLINE In-Process & Other Non-Indexed Citations (via OvidSP), MEDLINE Epub Ahead of Print (via OvidSP), MEDLINE Daily Update (via OvidSP), EMBASE (via OvidSP), Cochrane Database of Systematic Reviews [via Wiley Online Library (John Wiley & Sons, Inc., Hoboken, NJ, USA)], Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley Online Library), Database of Abstracts of Reviews of Effects (DARE) [via the Centre for Reviews and Dissemination (CRD)], Health Technology Assessment (HTA) database (via CRD), Science Citation Index and Conference Proceedings [via the Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA)] and the PROSPERO International Prospective Register of Systematic Reviews (via CRD)
- trial database – ClinicalTrials.gov
- reference lists of relevant reviews and included studies
- online resources of health services research organisations and regulatory bodies – International Network of Agencies for Health Technology Assessment (INAHTA), the US Food and Drug Administration (FDA) medical devices, FDA Clinical Laboratory Improvement Amendments (CLIA) database and European Commission medical devices
- online resources of selected professional societies and conferences – British Society for Antimicrobial Chemotherapy, British Infection Association, PHE, British Society for Antimicrobial Chemotherapy, Royal College of Pathologists, streptococcal biology conference, Lancefield International Symposium on Streptococci and Streptococcal Diseases, Federation of Infection Societies Conference, The European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Microbiology Society Conference, American Society of Microbiology, and Association of Clinical Biochemistry and Laboratory Medicine
- online resources of manufacturers of the included rapid tests.

Inclusion and exclusion of relevant studies (Boxes 1 *and* 2)

BOX 1 Inclusion criteria

Population

- People aged ≥ 5 years presenting with symptoms of an acute sore throat. Where possible, relevant subgroups evaluated included children (aged 5–14 years), adults (aged 15–75 years) and the elderly (adults aged > 75 years); however, mixed populations were acceptable. Studies of children aged < 5 years could be included providing ≥ 90% were above this age.

Intervention

- Point-of-care tests for strep A (including RADTs and molecular tests as described in *Tables 1* and *2*).

BOX 1 Inclusion criteria (*continued*)

Comparator

- Clinical scoring tools (such as FeverPAIN, Centor or McIsaac).

Reference standard

- Microbiological culture of throat swabs.

Outcome

- Outcomes of test performance:
  - test accuracy – sensitivity, specificity, PPV and NPV. Where possible, evaluated by relevant clinical scores (Centor/McIsaac $\geq$ 3 points and FeverPAIN $\geq$ 4 points)
  - discordant results with throat culture
  - test failure rates
  - time to antimicrobial prescribing decision
  - changes to antimicrobial prescribing decision
  - number of appointments required per episode
  - number of delayed or immediate antibiotic prescriptions issued.
- Clinical outcomes:
  - morbidity, including post-strep A infection complications, such as rheumatic fever and side effects from antibiotic therapy
  - mortality
  - contribution to antimicrobial stewardship and onward transmission of infection.
- Patient-reported outcomes:
  - health-related quality of life
  - patient satisfaction with test and antimicrobial prescribing decision
  - health-care professional satisfaction with test and antimicrobial prescribing decision.
- Costs.

Study design

For test accuracy data:

- clinical test accuracy studies that compare the index tests (point-of-care tests for strep A) with throat swab culture
- studies of head-to-head comparisons of rapid tests were eligible for inclusion if test accuracy statistics were reported for each test.

For data on other clinical outcomes:

- any study design comparing the index tests (point-of-care tests for strep A) and/or clinical scoring tools (Centor, McIsaac or FeverPAIN) with biological culture as a reference standard.

Health-care setting

- Primary care (GP clinics and walk-in centres), secondary care (urgent care/walk-in centres and emergency departments) or community pharmacy settings.

NPV, negative predictive value; PPV, positive predictive value.

BOX 2 Exclusion criteria

Population

- Patients without acute sore throat.
- Patients with existing comorbidities.
- Patients with known invasive strep A infection.

Intervention

- Other point-of-care tests that are not listed in the NICE scope.

Comparator

- For test accuracy data: no comparison of index test vs. throat culture reported.
- For other outcomes: no comparison of index test vs. throat culture or clinical scoring tools (Centor, McIsaac or FeverPAIN).

Study design

- Reviews, biological studies, case reports, editorials and opinions, poster presentations without supporting abstracts, non-English-language reports, meeting abstracts without sufficient information to produce 2 × 2 contingency tables for test performance.

Date

- Studies published before 1998 (keeping in line with the 1998 directive of the European parliament requiring all in vitro diagnostic devices to have a CE marking).[25]

Setting

- Hospital inpatient.

CE, Conformité Européenne.

Study selection strategy

All publications that were identified in searches from all sources were collated in EndNote (Clarivate Analytics) and deduplicated. Two reviewers independently screened the titles and abstracts of all records identified by the searches (Cohen's kappa = 0.997) and discrepancies were resolved through discussion. Full copies of all studies deemed potentially relevant were obtained and two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus or discussion with a third reviewer. Records excluded at full-text stage and reasons for exclusion were documented.

Data extraction strategy

All data were extracted by one reviewer, using a piloted data extraction form. A second reviewer checked the extracted data on test accuracy [2 × 2 table, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)], and a third reviewer checked other extracted data. Any disagreements were resolved by consensus. A sample data extraction form used in this review is available in *Appendix 2*. Test accuracy statistics for rapid/index tests were derived from data extracted onto 2 × 2 contingency tables in the format shown in *Table 3*. As shown, A represents the number of patients positive for strep A by rapid test and throat culture (true positives); B represents the number of patients positive for strep A by rapid test but not throat culture (false positives); C represents the number of patients negative for strep A by rapid test but positive by throat culture (false negatives); and D represents the number of patients negative for strep A by rapid test and throat culture (true negatives). Sensitivity was calculated as A/(A + C), specificity as D/(B + D), PPV as A/(A + B) and NPV as D/(C + D). Similarly, using data extracted in the formats shown in *Tables 4* and *5*, we calculated

TABLE 3 A 2 × 2 contingency table for rapid test vs. throat culture

	Culture +	Culture –	Total
Index test +	A	B	A + B
Index test –	C	D	C + D
Total	A + C	B + D	A + B + C + D

TABLE 4 A 2 × 2 contingency table for Centor/Modified Centor vs. throat culture

	Culture +	Culture –	Total
Centor/McIsaac score of ≥ 3 points	A	B	A + B
Centor/McIsaac score of < 3 points	C	D	C + D
Total	A + C	B + D	A + B + C + D

TABLE 5 A 2 × 2 contingency table for FeverPAIN vs. throat culture

	Culture +	Culture –	Total
FeverPAIN score of ≥ 4 points	A	B	A + B
FeverPAIN score of < 4 points	C	D	C + D
Total	A + C	B + D	A + B + C + D

accuracy statistics for the current pathway (Centor/McIssac/FeverPAIN scores) based on NICE thresholds. Where PCR techniques were employed to arbitrate discordant results between microbiological culture and rapid tests, we report the PCR results for the discordant cases. We also extracted test accuracy data for each index test with culture as the reference standard in studies of head-to-head (direct) comparisons of index tests. Data on other outcomes of test performance, morbidity, antibiotic-prescribing behaviour, population characteristics and settings were also extracted using the extraction form.

Quality assessment strategy for test accuracy studies

Quality assessment of eligible test accuracy studies was undertaken with a tailored Quality Assessment of Diagnostic Accuracy Studies – 2 (QUADAS-2) tool.[26] Methodological quality was assessed by a single reviewer and findings were checked by a second reviewer. Disagreements were resolved by consensus or use of a third reviewer.

Quality assessment aimed to assess the risk of bias and applicability concerns of included studies where one (or more) of our 21 scoped tests was the index test(s), and with biological throat culture as the reference standard. Additional tests outside the scope were not quality appraised.

Modifications to tailor the QUADAS-2 form to the research question in terms of the risk-of-bias assessment were as follows (see *Appendix 4* for the tailored QUADAS-2 form and guidance notes).

Patient selection domain

Two further signalling questions were added to this domain. The first was 'were selection criteria clearly described?'. It is important that the correct patient groups were included in the studies. Patients aged < 5 years follow a different NICE clinical pathway[27] because they are more likely to present with a sore throat and less likely to be able to articulate their symptoms, and it is less likely that a throat swab can be obtained. Likewise, a clinical score (such as Centor or FeverPAIN) should be reported, with patients included only if they have a score of > 3 points on Centor or > 4 points on FeverPAIN. Those with lower scores may be systematically different and, therefore, test accuracy may also differ, introducing bias. Including patients aged < 5 years and with a low clinical score also raises applicability concerns.

The second signalling question that was added was 'were patients seen in an ambulatory care setting?'. Patients seen as inpatients may vary in severity and have comorbidities affecting their diagnosis.

Index test domain

Two questions were added within this domain. The first was 'was a separate swab undertaken for the index test?'. This question was added as manufacturers' specifications require separate swabs to be taken for index and reference standard tests. Using one swab for multiple purposes may reduce the quantity of the sample for testing and, thus, affect the accuracy of the test. The second question was 'is the test reading objective?'. Some of the tests require a subjective reading of whether or not a line, indicating a positive result, has appeared. Owing to this, there is always a high level of bias in any rapid test that requires a determination of the result by the human reader. Tests with automated readings have been shown to have improved specificity and reduce operator errors, especially in unclear results.[28]

Comparator domain

One additional signalling question was added in this domain: 'was a separate swab taken for throat culture testing?'. Using one swab for multiple purposes may reduce the quantity of the sample for testing and, thus, affect the accuracy of the test. Under this domain, the directions for taking a throat culture specimen were clarified based on the PHE guidelines on *UK Standards for Microbiology Investigations*.[29]

Flow and timing

Two further signalling questions were added to the flow and timing domain. The first was 'were both index test(s) and reference standard (and comparator where included) all carried out at the same appointment?'. The swabs for a rapid test and culture should be obtained at the same appointment. The levels of strep A are likely to vary by day, so taking a later sample could introduce systematic bias.

The additional signalling question was 'were both index test(s) and reference standard (and comparator where included) all carried out prior to commencement of antibiotics?'. Patients should not have been treated with antibiotics prior to testing, as antibiotics are likely to have reduced the amount of strep A present.

Quality appraisal strategy for studies of prescribing behaviour and clinical outcomes

Quality appraisal for studies of prescribing behaviour and clinical outcomes used two different tools: the Cochrane risk-of-bias tool for randomised controlled trials (RCTs)[30] and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies.[31] Methodological quality was assessed by a single reviewer and findings were checked by a second reviewer. Disagreements were resolved by consensus or use of a third reviewer.

Assessment of test accuracy

To assess the accuracy of the point-of-care tests, we planned to conduct a series of meta-analyses on the available data. Data from studies that either presented 2 × 2 tables for one of the index tests compared with culture or provided information that allowed calculation of the 2 × 2 table were included in the meta-analyses.

The median age of participants was used to categorise each study into one of the three age groups of interest, with two reviewers discussing when the categorisation was not straightforward. Setting was also considered to inform the age categorisation where necessary (e.g. if the study was conducted within a paediatric department). The setting of each study was treated as a categorical variable, indicating primary care (health-care centre, GP clinic or primary care clinic), secondary care (emergency department, private paediatric clinic, outpatient clinic, urgent care clinic or walk-in centre) and pharmacy setting or mixed.

For the purpose of the meta-analysis, the throat score of the population was dichotomised to 0, if the study population included patients who had scores below the threshold set in the scope, and 1, if the study population matched the scope (Centor/McIsaac score of $\geq$ 3 points or FeverPAIN score of $\geq$ 4 points). Alternative throat score classification of study populations was also considered, using the categories of a population matching the scope (see *Chapter 1*, *Target population*), a population restricted by throat score but still including patients not in the scope (e.g. Centor score of 2 points) and a population without any restriction by throat score.

Methods of analysis/synthesis

We planned to use bivariate models to conduct each meta-analysis, as they allow simultaneous estimation of both sensitivity and specificity, accounting for correlation between the two measures. Where at least two studies existed for a test, we used a random-effects model to allow for deviation in test performance across each study. If bivariate or random-effects models failed to converge or produced results with unexpectedly wide confidence intervals (CIs) around key parameters, then simpler models (e.g. fixed-effect or univariate models) were used instead.[32,33] Where bivariate models were used, a comparison with the equivalent univariate models was made, and any difference noted. It was not anticipated that any meaningful difference between the two model types would be observed given the small number of data available.

For index tests that had just one study, a meta-analysis was not conducted. The impacts of age, setting and prevalence on test performance were all assessed through the meta-analysis of relevant subgroups. NICE advised the EAG against meta-analysis across rapid tests from different manufacturers.

Clinical effectiveness results

Search results

Figure 2 is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram that illustrates the study selection process for the clinical effectiveness review. The search identified 5919 records through database and other searches. Following duplicate removal, we screened 3309 records, of which 3072 were excluded by their titles and abstracts, leaving 237 assessed for their eligibility to be included in the review. A total of 199 studies were subsequently excluded with reasons, leaving 38 studies [26 full texts,[6,20,23,24,34–55] three abstracts,[56–58] five manufacturers' studies (submitted directly to NICE in response to a request for information) and four FDA documents[59–62]]. The most common reason for exclusion at this stage was not reporting any of the rapid tests listed in the scope. The full list of excluded studies with reasons for exclusion can be found in *Appendix 3*.

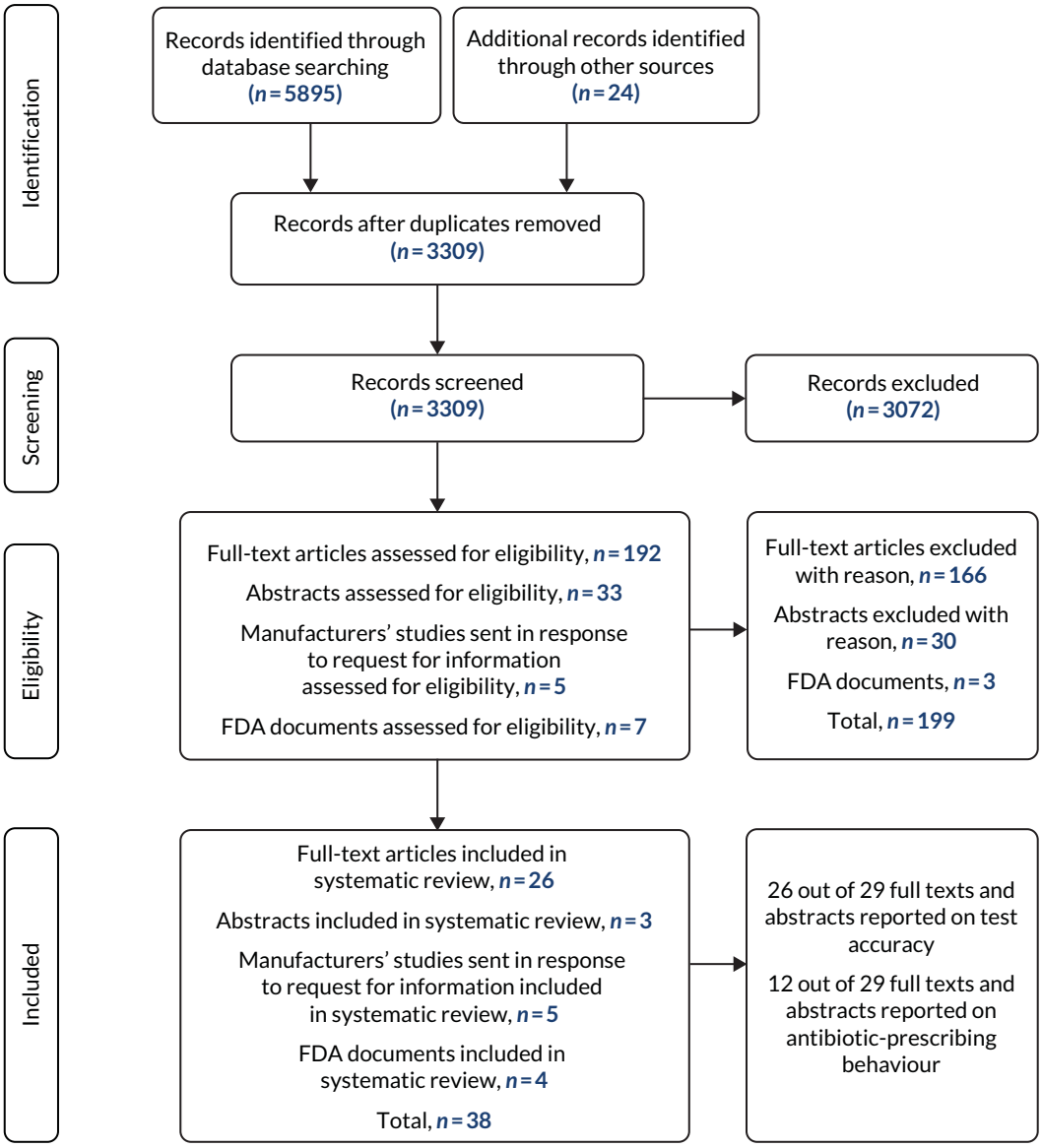

FIGURE 2 The PRISMA flow diagram showing study selection for the clinical effectiveness review.

Study characteristics

Characteristics of the 38 studies included in the clinical effectiveness review are described in *Figures 3* and *4* and *Table 6*. Of the 29 studies (full texts and abstracts)[6,20,23,24,34–58] identified by the search, 26 of the studies reported test accuracy data.[20,23,24,34–52,54,57,58,63] Three of the identified studies[6,53,55] reported only other outcomes (such as antibiotic-prescribing rates) and did not report test accuracy. In addition, five studies were sent by manufacturers in response to a request for information by NICE and four FDA documents were retrieved.[59–62]

The tests, their settings, the populations they cover and the head-to-head studies are illustrated in *Figures 3* and *4*.

Population

The 38 included studies comprised ≈ 14,000 symptomatic participants. Prevalence of strep A ranged from 15% to 49%, with no clear demographic or clinical patterns accounting for this variation.[39,56] Similarly, prevalence estimates of strep A were no more or less likely to be higher in secondary or primary care settings. The study population comprised adults and children; however, the exact proportions are unknown as they were not reported in about half of the included studies. In most of

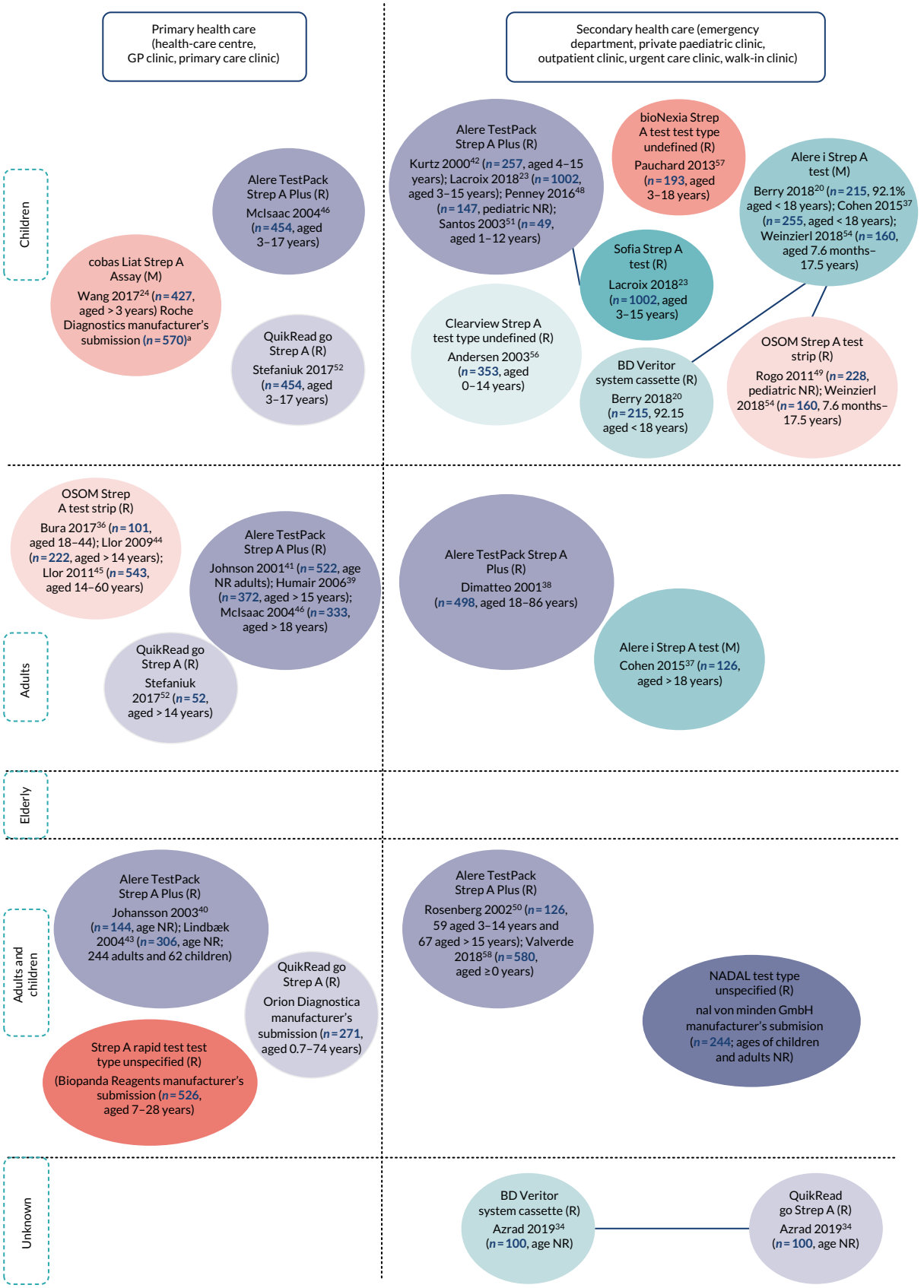

FIGURE 3 Diagram of studies by test type, setting and population for included test accuracy studies with extractable 2 × 2 data. Note that lines between tests indicate head-to-head (direct) comparisons. M, molecular test; NR, not reported; R, rapid test.

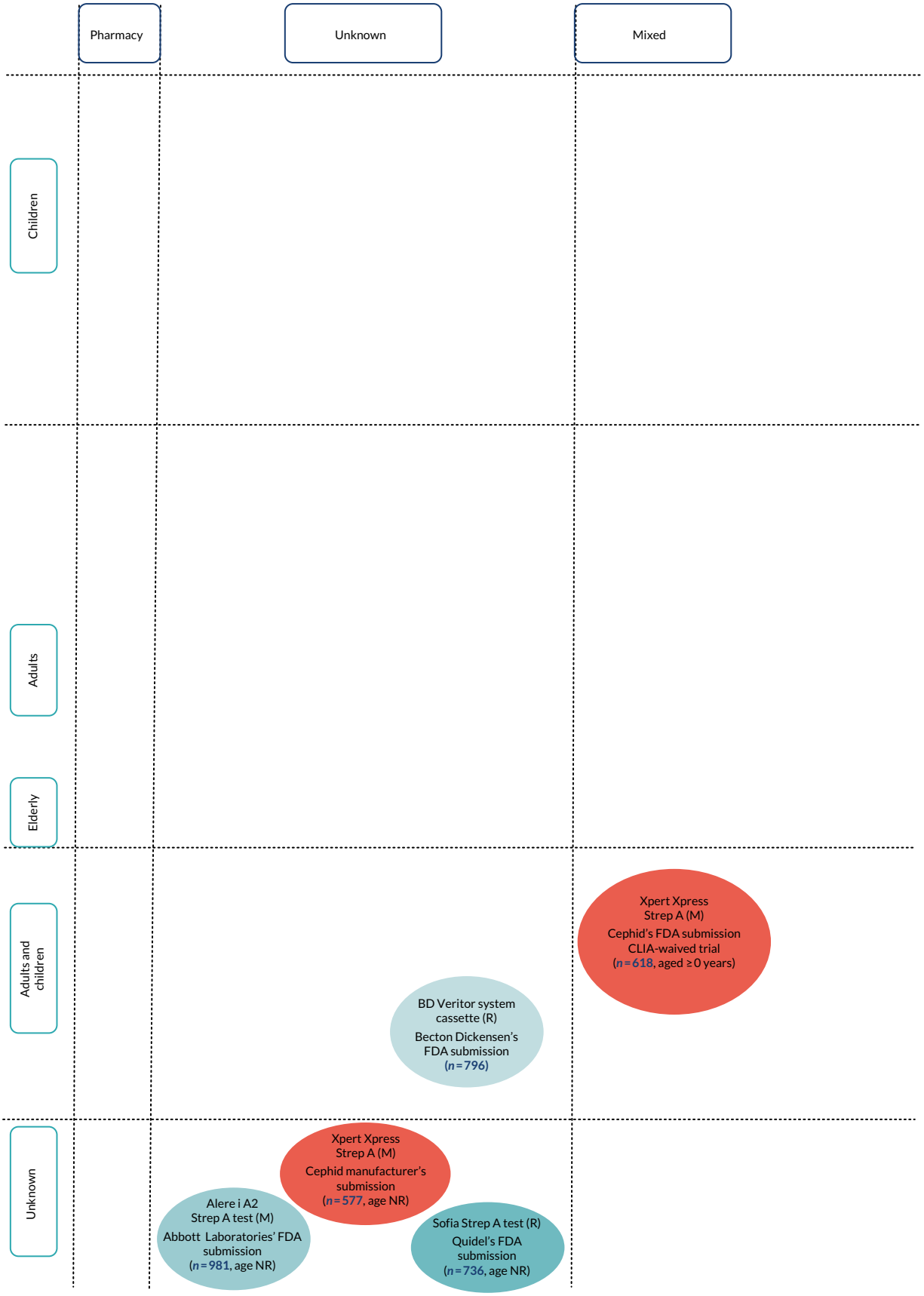

FIGURE 4 Diagram of studies by test type, setting and population for included test accuracy studies with extractable 2 × 2 data. M, molecular test; NR, not reported; R, rapid test.

TABLE 6 Characteristics of the included studies

Study (first author and year of publication)	Data source	Setting	Study population				Index test	Comparison with Centor/McIsaac/ FeverPAIN scores?	Throat swab culture medium	Outcomes	Test accuracy in high-risk subpopulations with Centor/McIsaac scores of ≥ 3 points or FeverPAIN score of ≥ 4 points
			n	Age group as reported	Sore throat clinical score criteria	Strep A prevalence (%)					
Published articles and abstracts											
Anderson 2003[56]	Abstract	Secondary	353	Children (0–14 years)	No criteria reported Used clinical symptoms	15	Clearview Strep A	No	NR	Test accuracy	NR
Azrad 2019[34]	Published article	Secondary	100	NR	No criteria reported Used clinical symptoms	25	BD Veritor system QuikRead Go Strep A test kit (Orion Diagnostica)	No	Streptococcal selective agar	Test accuracy	NR
Berry 2018[20]	Published article	Secondary	215	Children (age range not reported)	NR	19.5	Alere i Strep A test BD Veritor system	No	Blood agar	Test accuracy Antibiotic-prescribing behaviour	NR NR
Bird 2018[35]	Published article	Secondary	395	Children	McIsaac ≥ 3 points	NR or not calculable	bioNexia Strep A	Yes/Centor	NA	Test accuracy Antibiotic-prescribing behaviour	NR
Bura 2017[36]	Published article	Primary	101	Adults (18–44 years)	Centor ≥ 2 points	22.7	OSOM Strep A test (Sekisui Diagnostics)	Yes/Centor	Blood agar	Test accuracy Antibiotic-prescribing behaviour	No
Cohen 2015[37]	Published article	Secondary	481	Children (median age 11 years)	McIsaac all scores	30.3	Alere i Strep A test	Yes/McIsaac	Blood agar	Test accuracy	No
Dimatteo 2001[38]	Published article	Secondary	383	Adults (18–86 years)	Centor ≥ 1 point	NR or not calculable	Alere™ TestPack +Plus Strep A (Abbott Laboratories)	Yes/McIsaac	Streptococcal selective agar	Test accuracy	NR
Humair 2006[39]	Published article	Primary	224	Adults (15–65 years)	Centor = 2 points Centor > 2 points	46.9	Alere TestPack +Plus Strep A (Abbott Laboratories)	Yes/Centor	Blood agar	Test accuracy Antibiotic-prescribing behaviour	Yes
Johansson 2003[40]	Published article	Primary	144	Mixed (children and adults)	NR	31.4	Alere TestPack +Plus Strep A (Abbott Laboratories)	No	NR	Test accuracy Antibiotic-prescribing behaviour	NR

Study (first author and year of publication)	Data source	Setting	Study population: *n*	Study population: Age group as reported	Study population: Sore throat clinical score criteria	Study population: Strep A prevalence (%)	Index test	Comparison with Centor/McIsaac/ FeverPAIN scores?	Throat swab culture medium	Outcomes	Test accuracy in high-risk subpopulations with Centor/McIsaac scores of ≥ 3 points or FeverPAIN score of ≥ 4 points
Johnson 2001[41]	Published article	Primary	522	Adults (median age 26 years)	No criteria reported Used clinical symptoms	NR or not calculable	Alere TestPack +Plus Strep A (Abbott Laboratories)	No	Blood agar	Test accuracy	NR
Kurtz 2000[42]	Published article	Secondary	257	Children (4–15 years)	No criteria reported Used clinical symptoms	31.1	Alere TestPack +Plus Strep A (Abbott Laboratories)	No	Blood agar	Test accuracy	NR
Lacroix 2018[23]	Published article	Secondary	1002	Children	McIsaac ≥ 2 points	38	Sofia Strep A FIA (Quidel) Alere TestPack +Plus Strep A test (Abbott Laboratories)	No	Blood agar	Test accuracy	No
Lindbæk 2004[43]	Published article	Primary	306	Adults (median age 23.9 years)	NR	35.9	Alere TestPack +Plus Strep A (Abbott Laboratories)	No	Streptococcal selective agar	Test accuracy	NR
Little 2013[6]	Published article	Primary	1760	Mixed (aged ≥ 3 years)	FeverPAIN ≥ 1 point	NR or not calculable	Alere TestPack +Plus Strep A (Abbott Laboratories)	Yes	None	Antibiotic-prescribing behaviour	No
Llor 2009[44]	Published article	Primary	222	Adults (median age 30.6 years)	Centor ≥ 2 points	21.2	OSOM Strep A	Yes/Centor	Blood agar	Test accuracy	No
Llor 2011[45]	Published article	Primary	276	Adults (median age 31.7 years)	Centor ≥ 1 point	16.7	OSOM Strep A test	Yes/Centor	Blood agar	Test accuracy Antibiotic-prescribing behaviour	Yes
McIsaac 2004[46]	Published article	Primary	787	Children (3–17 years) and adults (≥ 18 years); results reported separately by group	McIsaac all scores	29	TestPack Plus Strep A test (Abbott Laboratories)	Yes/McIsaac	Blood agar	Test accuracy Antibiotic-prescribing behaviour	No
Nerbrand 2002[47]	Published article	Primary	615	Mixed (children and adults	No criteria reported Used clinical symptoms	21.1	TestPack Plus Strep A test (Abbott Laboratories)	No	Blood agar	Test accuracy	NR

continued

TABLE 6 Characteristics of the included studies (*continued*)

Study (first author and year of publication)	Data source	Setting	Study population				Index test	Comparison with Centor/McIsaac/ FeverPAIN scores?	Throat swab culture medium	Outcomes	Test accuracy in high-risk subpopulations with Centor/McIsaac scores of ≥ 3 points or FeverPAIN score of ≥ 4 points
			n	Age group as reported	Sore throat clinical score criteria	Strep A prevalence (%)					
Pauchard 2013[57]	Abstract	Secondary	193	Children (3–18 years)	McIsaac > 2 points	37	Strep A Rapid Test (Biopanda Reagents)	Yes/McIsaac	NR	Test accuracy	NR
Penney 2016[48]	Published article	Secondary	147	Children (mean age 8.8 years)	No criteria reported Used clinical symptoms	40.1	Alere TestPack +Plus Strep A test (Abbott Laboratories)	No	Streptococcal selective agar	Test accuracy	NR
Rogo 2011[49]	Published article	Secondary	228	Children	No criteria reported Used clinical symptoms	28.9	OSOM Strep A test	No	Blood agar	Test accuracy	NR
Rosenberg 2002[50]	Published article	Secondary	126	Mixed (children and adults)	Centor all scores	25.4	TestPack Plus Strep A test (Abbott Laboratories)	Yes/Centor	Blood agar	Test accuracy Antibiotic-prescribing behaviour	NR
Santos 2003[51]	Published article	Secondary	49	Children (1–12 years)	No criteria reported Used clinical symptoms	30	Alere TestPack +Plus Strep A (Abbott Laboratories)	No	Blood agar	Test accuracy	NR
Stefaniuk 2017[52]	Published article	Primary	44	Children	McIsaac/Centor all scores	26.3	QuikRead Go Strep A test kit (Orion Diagnostica)	Yes/Centor	Blood agar	Test accuracy	No
			96	Adults and children	McIsaac/Centor all scores	22.4				Antibiotic-prescribing behaviour	
Thornley 2016[53]	Published article	Pharmacy	149	NR	Centor > 2 points	24.2	OSOM Strep A test (Sekisui Diagnostics)	Yes/Centor	None	Antibiotic-prescribing behaviour	NA
Valverde 2018[58]	Abstract	Secondary	580	Mixed (aged ≥ 0 years)	NR	NR or not calculable	TestPack Plus Strep A test	No	Blood agar	Test accuracy	NR
Wang 2017[24]	Published article	Primary	427	Children	Centor ≥ 1 point	30.2	cobas Liat Strep A Assay (Roche Diagnostics)	No	NR	Test accuracy	No
Weinzierl 2018[54]	Published article	Secondary	160	Children (median age 6.5 years)	NR	38	OSOM Strep A test Alere i Strep A test	No	Blood agar	Test accuracy	NR
Worrall 2007[55]	Published article	Primary	533	NR	Centor all scores	NR or not calculable	Clearview Exact Strep A (Abbott Laboratories)	Yes/Centor	NA	Antibiotic-prescribing behaviour	NA

Study (first author and year of publication)	Data source	Setting	Study population				Index test	Comparison with Centor/McIsaac/ FeverPAIN scores?	Throat swab culture medium	Outcomes	Test accuracy in high-risk subpopulations with Centor/McIsaac scores of ≥ 3 points or FeverPAIN score of ≥ 4 points
			n	Age group as reported	Sore throat clinical score criteria	Strep A prevalence (%)					
Manufacturer's studies provided in responses to request by NICE											
Biopanda Reagents	Manufacturer's information	Secondary	160	Median age 6.5 years	NA	23.2	Alere i Strep A test	No	Blood agar	Test accuracy	NR
Cepheid	Manufacturer's information	Primary	577	NR	NA	25.6	Xpert Xpress	Yes/Centor	NA	Test accuracy	NR
nal von minden GmbH	Manufacturer's information	Unknown	244	Mixed (adults and children)	NA	34.4	NADAL Strep A test	No	Blood agar	Test accuracy	NR
Orion Diagnostica	Manufacturer's information	Primary	271	NR	NA	32.8	QuikRead Go Strep A test kit (Orion Diagnostica)	No	Streptococcal selective agar	Test accuracy	NR
Roche Diagnostics	Manufacturer's information	Mixed	570	Mixed (aged ≥ 3 years)	NA	30.4	cobas Liat Strep A Assay (Roche Diagnostics)	No	Blood agar	Test accuracy	NR
FDA documents											
Abbott Laboratories[61]	FDA document	Mixed	981	NR	NA	20.2	Alere i Strep A 2 test	No	Blood agar	Test accuracy	NR
Becton Dickinson[59]	FDA document	Mixed	796	Mixed (aged ≥ 0 years)	NA	18.7	BD Veritor system	No	Blood agar	Test accuracy	NR
Cepheid[62]	FDA document	Mixed	618	NR	NA	25.6	Xpert Xpress Strep A (Cepheid)	No	NR	Test accuracy	NR
Quidel[60]	FDA document	Mixed	736	NR	NA	17.4	Sofia Strep A FIA (Quidel)	No	Blood agar	Test accuracy	NR

FIA, fluorescent immunoassay; NA, not applicable; NR, not reported.

the included studies, participants aged < 18 years were identified as children. In fact, only two studies met the age criterion for children (ages 5 to 14 years) as defined in the protocol and scope.[50,51] Hence, studies that included children aged < 5 years as well as ≥ 5 years were included in the present review. More so, only two studies met the age criterion for adults (age ≥ 15 years) as defined in the protocol and scope and, therefore, the findings of the review may be applicable to only a mixed population.[39,52]

All 38 studies included patients with a sore throat; however, other clinical characteristics were insufficiently reported across most of the included studies. For instance, sore throat clinical scores (e.g. Centor/McIsaac/FeverPAIN scores) were reported in 16 studies,[6,23,35–39,44–46,50,52,53,55,57] of which two exclusively included patients with high clinical scores (i.e. Centor ≥ 3 points, FeverPAIN ≥ 4 points).[6,53] Both of these studies were on prescribing behaviours. However, there were two test accuracy studies that included patients with lower clinical scores (i.e. Centor scores of < 3 points) but reported test accuracy results separately by Centor score.[39,45]

Recent antibiotic use prior to enrolment was considered in eight included studies, and patients without any recent use of antibiotics prior to recruitment were eligible for inclusion in these studies.[24,35,36,42,45,47,48,50]

Index tests

There were more studies evaluating RADTs (76%, 29/38) than were evaluating molecular tests (18%, 7/38) or studies comparing both rapid tests and molecular tests (5%, 2/38). For instance, the Alere™ TestPack +Plus Strep A (Abbott Laboratories) was the most common antigen detection test, which was evaluated in 13 studies (excluding unpublished studies conducted by the manufacturers).[6,23,38–43,46–48,51,58] Conversely, the only molecular test evaluated in a peer-reviewed journal article was the PCR-based cobas Liat Strep A Assay (Roche Diagnostics).[24]

As shown in *Table 6*, there were four studies providing head-to-head comparisons of index tests: BD Veritor System (Becton Dickinson) and QuikRead Go (Orion Diagnostica);[34] Alere i Strep A (Abbott Laboratories) and BD Veritor System (Becton Dickinson);[20] Alere i Strep A (Abbott Laboratories) and Sofia Strep A fluorescent immunoassay (FIA) (Quidel);[23] and Alere i Strep A (Abbott Laboratories) and OSOM Strep A.[54] Essentially, each index test was compared with throat culture as the reference standard in order to obtain test accuracy.

The search strategy revealed test accuracy studies of OSOM Ultra Strep A (Sanofi Genzyme and Sekisui Diagnostics).[64,65] However, these studies were subsequently excluded because the EAG could not confirm whether it is the same as the OSOM Strep A test (Genzyme and Sekisui Diagnostics), which is listed among the scoped rapid tests. Similarly, it was unclear if Sofia Strep A+ Plus FIA (Quidel)[66] and OSOM Strep A (Sekisui Diagnostics)[67] were identical to Sofia Strep A FIA (Quidel) and OSOM Strep A (Sekisui Diagnostics), respectively; hence, studies of the former were excluded.

Comparator and reference standard

Index tests were compared with Centor, McIsaac or FeverPAIN scoring tools in 12 studies.[6,35,36,38,45,46,50,52,53,55,57,68] However, only six of these studies directly compared test accuracy between clinical scoring tools and point-of-care tests.[39,44–46,52] Only two reported test accuracy in patients with high clinical scores (Centor ≥ 3 points, FeverPAIN ≥ 4 points).[39,45]

The culture medium used for the reference standard (blood agar or streptococcal selective agar) was reported in all but five studies.[24,40,56,57] Neither the manufacturers' submissions (submitted directly to NICE in response to a request for information) nor the FDA studies provided information on index tests compared with clinical scoring tools.

Outcomes

Thirty-eight studies were included across all outcomes. Twenty-six published articles (full texts and abstracts) reported test accuracy data (of which seven also reported on antibiotic-prescribing rates

and five reported on test failure rate); there were an additional five submissions from manufacturers and four FDA documents.

Five studies had insufficient data to construct 2 × 2 contingency tables to ascertain the accuracy of index tests with microbiological throat culture as the reference standard.[6,35,47,53,55] These studies were further excluded from the assessment of test accuracy in *Point-of-care/index tests*. An attempt to verify at least some of the discrepant results between rapid tests and microbiological culture was undertaken in only five studies.[20,23,24,37,43] Antibiotic-prescribing behaviour was reported in 12 studies.[6,20,35,36,39,40,45,46,50,52,53,55] None of the other outcomes in the scope or protocol was reported in any of the included studies.

Setting

Participants in the included studies were recruited from GP/primary care clinics/family practices,[6,40,41,43–47] community pharmacies,[53] paediatric clinics,[42,49,54,56] paediatric emergency departments,[23,48,57] hospital outpatient departments[20,51] and emergency departments.[35,50] There were two multicentre studies with mixed populations from primary and secondary care settings: Cohen *et al.*[37] sampled patients from the emergency department (secondary care) and urgent care clinics (primary care); and Wang *et al.*[24] sampled patients from paediatric clinics (secondary care) and family practices (primary care).

Only one unpublished study supplied by the manufacturers confirmed the study setting (Orion Diagnostica, primary care). The remaining unpublished studies conducted by manufacturers may have included mixed populations from primary and secondary care settings; however, this is purely speculative as study settings were not reported in these studies. However, these studies provide no evidence to suggest any recruitment of inpatients.

Study design

The 26 published studies on test accuracy comprised one RCT[45] and 25 cohort studies.[20,23,24,34–44,46,48–52,55–58,69] It was unclear what study design had been undertaken in any of the unpublished studies provided by the manufacturers or the FDA.

The 12 studies that provided data on antibiotic-prescribing rates comprised three RCTs,[6,45,55] one before-and-after cohort study[20] and eight one-armed cohort studies.[35,36,39,40,46,50,52,53]

Quality considerations of included studies

The assessment of risk of bias and applicability for the 26 included test accuracy studies[20,23,24,34–46,48–52,55–58,69] using the QUADAS-2 tool are summarised in *Table 7* and *Figure 5*. Four of the included studies compared two index tests that are relevant to this review, so there are 30 quality assessment ratings for the index test domains. Likewise, one study included two different culture mediums as its reference standard, so there are 27 quality assessment ratings across the reference standard domains.

Risk of bias for test accuracy studies

In general, the methodological and reporting quality of the included studies was poor, with risk of bias considered to be high in two or more domains for 13 studies (50%).[20,34–36,38,40–43,46,49–51] No study was considered to be at a low risk of bias in all four domains.

In 65.4% of studies (17/26),[20,23,24,35,37,42,43,46,47,49,51,52,54,56–58,70] it was not clear whether patients were consecutively included or a convenience sample had been chosen, and only 15.4% (4/26 studies)[39,44,45,48] were rated as having a low risk of bias in the patient selection domain (domain 1: patient selection). The selection process in the remaining 19.2% of studies (5/26)[34,36,41,50] was rated as being at a high risk of bias, with studies clearly reporting convenience samples, having case–control designs or having made inappropriate exclusions from the eligible screening population.

TABLE 7 Judgement of risk of bias and applicability of included studies

	Risk of bias						Applicability concerns				
Study (first author and year of publication)	Patient selection	Index test	Additional index test	Reference standard	Additional reference standard	Flow and timing	Patient selection	Index test	Additional index test	Reference standard	Additional reference standard
Andersen 2003[56]	Unclear	High	NA	Unclear	NA	Unclear	High	Unclear	NA	Unclear	NA
Azrad 2019[34]	High	Low	Low	Unclear	NA	High	High	Low	Low	Unclear	NA
Berry 2018[20]	Unclear	High	Low	High	NA	Unclear	High	Low	Low	Unclear	NA
Bird 2018[35]	Unclear	High	NA	Unclear	NA	High	High	Unclear	NA	Unclear	NA
Bura 2017[36]	High	High	NA	Low	NA	High	High	Low	NA	Low	NA
Cohen 2015[37]	Unclear	Low	NA	Low	NA	Unclear	High	Low	NA	Low	NA
Dimatteo 2001[38]	High	High	NA	High	NA	High	Low	Unclear	NA	High	NA
Humair 2006[39]	Low	High	NA	Unclear	NA	Low	Low	Low	NA	Low	NA
Johansson 2003[40]	Unclear	High	NA	Unclear	NA	High	High	Unclear	NA	Unclear	NA
Johnson 2001[41]	High	High	NA	High	NA	High	High	Low	NA	High	NA
Kurtz 2000[42]	Unclear	High	NA	High	Low	Unclear	High	Low	NA	High	Low
Lacroix 2018[23]	Unclear	Low	High	Low	NA	Low	High	Low	Low	Low	NA
Lindbæk 2004[43]	Unclear	High	NA	High	NA	Low	High	Low	NA	High	NA
Llor 2009[44]	Low	High	NA	Unclear	NA	Low	High	Low	NA	Unclear	NA
Llor 2011[45]	Low	High	NA	Unclear	NA	Unclear	Low	Low	NA	Low	NA
McIsaac 2004[46]	Unclear	High	NA	Low	NA	High	Unclear	Unclear	NA	Low	NA
Nerbrand 2002[47]	Unclear	High	NA	Unclear	NA	Low	High	Low	NA	Low	NA

Study (first author and year of publication)	Risk of bias						Applicability concerns				
	Patient selection	Index test	Additional index test	Reference standard	Additional reference standard	Flow and timing	Patient selection	Index test	Additional index test	Reference standard	Additional reference standard
Pauchard 2013[57]	Unclear	High	NA	Unclear	NA	Unclear	High	Unclear	NA	Unclear	NA
Penney 2016[48]	Low	High	NA	Unclear	NA	Low	High	Low	NA	Unclear	NA
Rogo 2011[49]	Unclear	High	NA	High	NA	Unclear	High	Low	NA	Unclear	NA
Rosenberg 2002[50]	High	High	NA	Low	NA	Low	High	Low	NA	Low	NA
Santos 2003[51]	Unclear	High	NA	Unclear	NA	High	High	Low	NA	Low	NA
Stefaniuk 2017[52]	Unclear	Low	NA	Unclear	NA	Unclear	High	Low	NA	Low	NA
Valverde 2018[58]	Unclear	High	NA	Low	NA	Unclear	High	Unclear	NA	Low	NA
Wang 2017[24]	Unclear	Low	NA	Unclear	NA	Low	High	Low	NA	Unclear	NA
Weinzierl 2018[54]	Unclear	Low	High	Low	NA	Unclear	High	Unclear	Unclear	Low	NA

NA, not applicable (the study did not have this additional test).

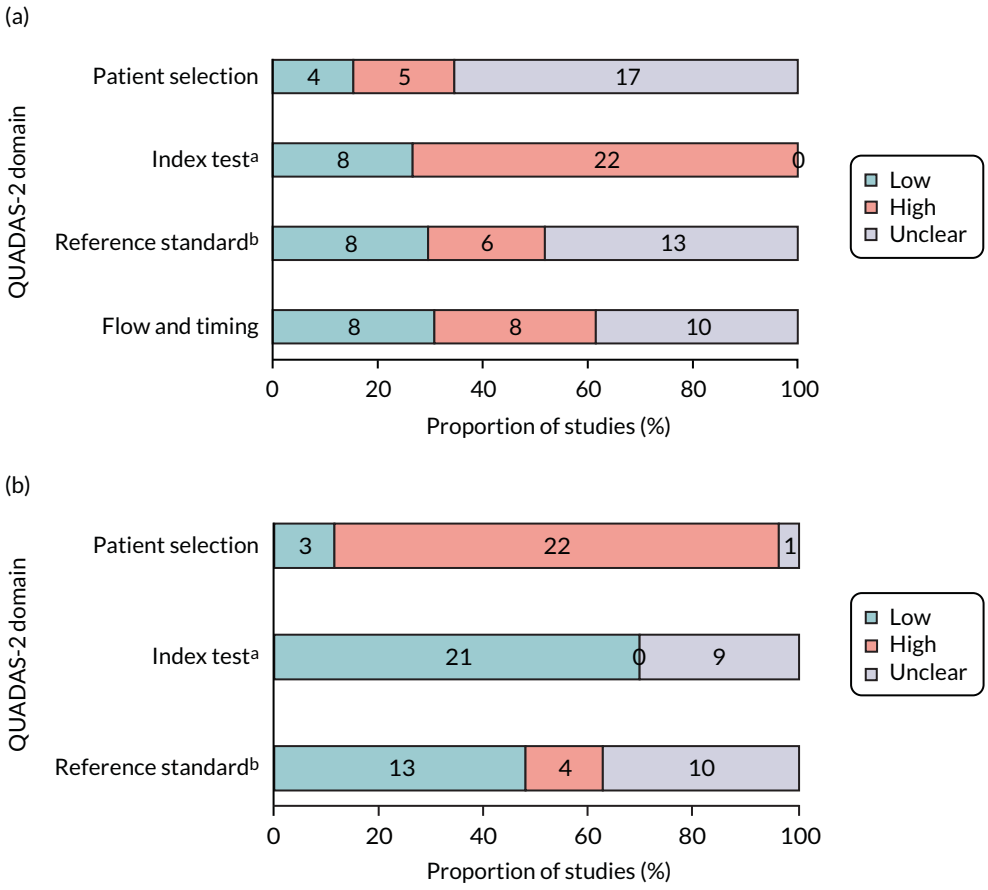

FIGURE 5 Concerns regarding bias and applicability in included studies. (a) Risk of bias; and (b) concerns regarding applicability. a, Four studies included two index tests relevant to this review; b, one study included two reference standards (culture methods) relevant to this review.

The key risks of bias were surrounding how the index test was undertaken (22/30 domains were rated as being at high risk, 73.3%, 22/26 studies).[20,23,35,36,38–46,48–51,55–58,69] Although all of the included studies were on predeveloped tests that had in-built thresholds, in many cases use of the index test required a subjective reading by a clinician (domain 2: index tests). There were further concerns that studies often used the same swab intended for the index test to first streak the agar for biological culture, rather than taking an additional swab sample. Using one swab for multiple purposes may reduce the amount of the sample and underestimate the accuracy of the test.

Unclear or incomplete reporting was common in the reference standard domain (domain 3: reference standard). In all studies, time taken to process the biological culture exceeded that of the rapid test, with biological cultures generally reported 48 hours following sample collection. However, many studies did not state that laboratory staff were blinded to the results of the index test or reference standard (domain 3: reference standard, 13/27 studies, 48.1%).[24,34,35,39,40,44,45,47,48,51,52,56,57] There was a high risk of bias in 22.2% of the studies (6/27)[20,38,41–43,49] because the methods of biological culture testing did not match current UK guidelines.[29]

The flow of patients through the studies was rated as being at a high risk of bias in 31% of studies (8/26, domain 4: flow and timing).[34–36,38,40,41,46,51] The majority of these (62.5%, 5/8 studies)[34–36,41,46,51] had incomplete testing and made exclusions from the analysis. However, in two of these studies only some patients received the reference standard (partial verification bias). In one study,[38] only patients with negative rapid test results received the reference standard; in the other,[40] only those with positive rapid test results were given the reference standard. The use of antibiotics was a further concern, with one study directly reporting 61 patients taking antibiotics at the time of testing,[34] and 90% (9/10) of unclear ratings were linked to prior/current antibiotic use not being reported.[20,37,42,45,49,52,54,56–58]

Applicability of study findings for test accuracy studies

The applicability of study findings was assessed with regard to three domains: patient selection, index test (rapid or molecular test) and reference standard (biological culture). There were significant concerns regarding the applicability of the studies to UK practice for patient selection in 22 of the 26 studies (85%, domain 1: patient selection).[20,23,24,34–37,40–44,48–52,55–58,69] In the UK, the test would be given only following an assessment using a clinical scoring tool, such as Centor or FeverPAIN. The rapid test would be given only to people with Centor scores of $\geq$ 3 points and FeverPAIN scores of $\geq$ 4 points. In all 22 studies, either a clinical scoring tool was not used or, if used, patients were included with scores lower than UK cut-off points and test accuracy data were not reported separately by score. In addition, 17 of the 22 studies (77%)[20,23,24,35,37,40,42,48–52,55–58,69] included children aged $<$ 5 years. Children aged $<$ 5 years follow a different clinical pathway owing to differences in the presentation of symptoms and difficulties around communication and sample collection.[27] Concerns regarding the applicability of the index test were rated as being low for the majority of the studies (21/30 domains, 70%, 18 studies),[20,23,24,34,36,37,39,41–45,48–52,69] with studies reporting that the tests were carried out in accordance with manufacturer's guidelines. The eight remaining studies[35,38,40,46,54,56–58] were rated as being unclear as this was not specified (domain 2: index test). Only four studies (4/27, 14.8%)[38,40,42,43] were rated as having high concern for the applicability with respect to the reference standard (owing to deviations from UK guidelines on the undertaking of appropriate culture methods with respect to agar type, incubation period or atmosphere; domain 3: reference standard).

Assessment of studies of prescribing behaviour and clinical outcomes

There were 12 studies that reported on antibiotic-prescribing behaviour.[6,20,35,36,39,40,45,46,50,52,53,55] Of these, three studies were RCTs[6,45,55] and were quality appraised using the Cochrane risk-of-bias tool for RCTs.[30] There were six studies (including one before-and-after study) that were single-arm cohorts and have been appraised using the JBI critical appraisal checklist[31] for analytical cross-sectional studies.[20,36,40,50,52,71] The remaining three studies were one-armed cohort studies using predetermined guidelines to hypothetically estimate prescribing behaviour and offer no information on what happened in the real world or on what clinicians would do.[39,46,53] These studies were not quality appraised and have been briefly summarised later in the results (see *Antibiotic-prescribing behaviours: other study designs*).

Randomised controlled trials

Risk of bias of the included trials is shown in *Figure 6* and *Table 8*. The domains regarding blinding were removed, as we were interested in test–treat trials measuring prescribing decisions with and without rapid tests. Therefore, clinicians could not be blinded to test results, and we considered blinding to which exact test was used to be unnecessary in this context. In general, the methodological quality of the RCTs was rated as being fair, with all studies having at least one domain rated as unclear. There was unclear risk of bias in four domains across the three studies (random sequence generation,

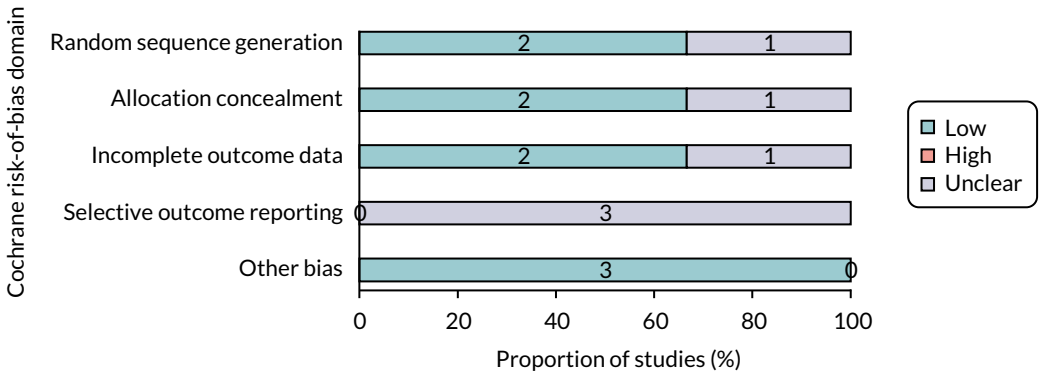

FIGURE 6 Concerns regarding the risk of bias of included RCTs.

TABLE 8 Judgement of risk of bias of included RCTs

Study (first author and year of publication)	Risk of bias				
	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective outcome reporting	Other bias
Little 2013[6]	Low	Low	Unclear	Unclear	Low
Llor 2011[45]	Low	Low	Low	Unclear	Low
Worrall 2007[55]	Unclear	Unclear	Low	Unclear	Low

allocation concealment, incomplete outcome data and selective outcome reporting). This was owing to insufficient information presented on which to make an assessment. The remaining applicable domains were judged to be at a low risk of bias.

Cohort studies

Risk of bias in the included cohort studies is shown in *Figure 7* and *Table 9*. No study was rated as having had high methodological quality across all areas. There was low methodological quality regarding criteria for inclusion in 83% of studies (five out of six) and details regarding the study subjects in 33% of studies two out of six).[20,35,40,50,52] These studies reported the details of the patients, but provided no information on the details of those who are making the prescribing decisions. The outcome of interest in these studies was prescribing behaviour. The measurement of prescribing behaviour considered to be valid and reliable was recording in medical records; only 33% of the studies clearly reported this.[20,36] A confounder in the studies was current antibiotic use; 33% (two out of six) of studies did not clearly specify current or recent antibiotic use as an excluding factor.

Current pathway (clinical scoring tools only)

Accuracy of clinical scoring tools with culture as the reference standard

Accuracy statistics for Centor[39,44,45,52] and McIsaac scores[46,52,57] with microbiological culture as the reference standard are presented in *Table 10*. The results show wide variations in the test accuracy of sore throat clinical scoring tools. Specificity point estimates were reported between 0.172 and 0.648, and sensitivity point estimates were reported between 0.735 and 0.972. This suggests that these tools might be better at identifying people who do have *Streptococcus* than they are at identifying people who do not.

Rosenberg *et al.*[50] and Johansson *et al.*[40] also reported accuracy statistics for sore throat symptoms with culture as the reference standard. However, these studies provided insufficient data to construct 2 × 2 contingency tables using the recommended clinical scoring threshold (see *Data extraction strategy*). The use of different clinical scoring tools, age selection criteria, clinical score inclusion criteria and settings across the seven contributing studies precluded any pooling.

Accuracy of clinical scoring tools split by age group

Two[46,52] of the six studies included a mixed population of adults and children. In the study by McIsaac *et al.*,[46] a threshold of > 2 points (Modified Centor/McIsaac score) produced a sensitivity estimate of 0.884 (95% CI 0.820 to 0.928) and a specificity estimate of 0.234 (95% CI 0.188 to 0.287) in children aged 3–17 years, and a sensitivity estimate of 0.767 (95% CI 0.651 to 0.858) and a specificity estimate of 0.439 (95% CI 0.378 to 0.501) in adults aged ≥ 18 years.

In the study by Stefaniuk *et al.*,[52] a threshold of > 2 points (Modified Centor/McIsaac score) produced a sensitivity estimate of 1.00 (95% CI 0.80 to 1.00) and a specificity estimate of 0.083 (95% CI 0.015 to 0.285) in children aged 1–14 years, and a sensitivity estimate of 0.739 (95% CI 0.513 to 0.889) and

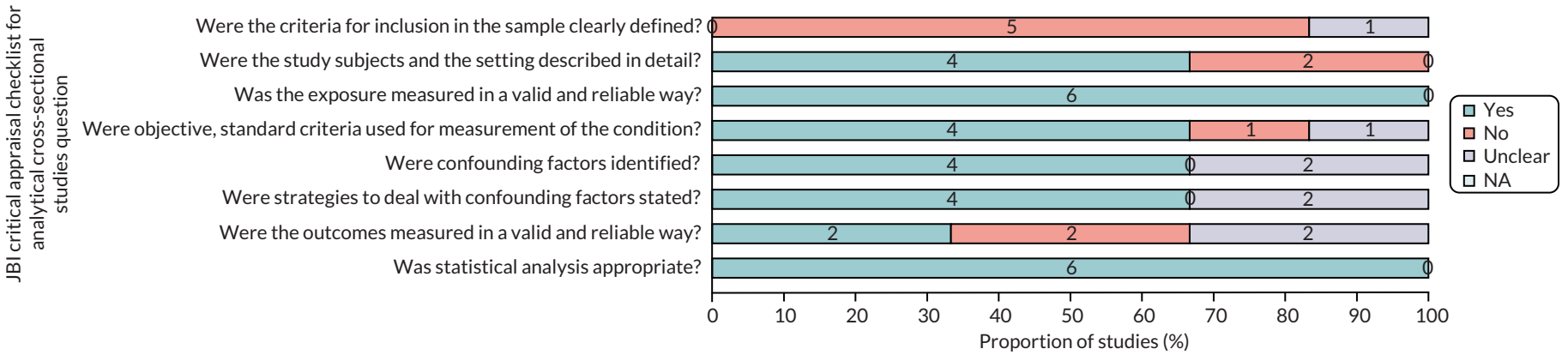

FIGURE 7 Methodological quality of included analytical cross-sectional studies. NA, not applicable.

TABLE 9 Judgement of risk of bias of included non-RCT studies

Study (first author and year of publication)	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was statistical analysis appropriate?
Berry 2018[20]	No	Yes	Yes	No	Unclear	Unclear	Yes	Yes
Bird 2018[35]	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Bura 2017[36]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Johansson 2003[40]	No	No	Yes	Unclear	Yes	Yes	No	Yes
Rosenberg 2002[50]	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Stefaniuk 2017[52]	No	No	Yes	Yes	Unclear	Unclear	Unclear	Yes

TABLE 10 Accuracy of clinical scores with culture as the reference standard

Study (first author and year of publication)	Strep A prevalence (%)	Setting	Clinical score	Test accuracy statistics				
				Culture +	Culture –	Total	Sensitivity (95% CI)	Specificity (95% CI)
Humair 2006[39]	46.9	Primary care/ GP clinic	Centor score of ≥ 3 points	105	119	224	0.750 (0.678 to 0.822)	0.487 (0.423 to 0.551)
			Centor score of < 3 points	35	113	148		
			Total	140	232	372		
Llor 2009[44]	21.2	Primary care/ GP clinic	Centor score of ≥ 3 points	47	104	151	0.855 (0.761 to 0.948)	0.377 (0.304 to 0.451)
			Centor score of < 3 points	8	63	71		
			Total	55	167	222		
Llor 2011[45]	16.7	Primary care/ GP clinic	Centor score of ≥ 3 points	36	80	116	0.735 (0.587 to 0.846)	0.648 (0.581 to 0.709)
			Centor score of < 3 points	13	147	160		
			Total	49	227	276		
McIsaac 2004[46]	29	Primary care/ GP clinic	McIsaac score of ≥ 3 points	193	375	568	0.846 (0.800 to 0.893)	0.329 (0.290 to 0.368)
			McIsaac score of < 3 points	35	184	219		
			Total	228	559	787		
Pauchard 2013[57]	37	Hospital	McIsaac score of ≥ 3 points	69	101	170	0.972 (0.893 to 0.995)	0.172 (0.112 to 0.253)
			McIsaac score of ≤ 2 points	2	21	23		
			Total	71	122	193		
Stefaniuk 2017[52]	22.4	Primary care/ GP clinic	Centor/McIsaac score of ≥ 3 points	37	39	76	0.861 (0.714 to 0.942)	0.250 (0.145 to 0.392)
			Centor/McIsaac score of ≤ 2 points	6	13	19		
			Total	43	52	95		

a specificity estimate of 0.414 (95% CI 0.241 to 0.609) in participants aged ≥ 15 years. As previously discussed (see *Population*), this overlap across age groups potentially limits subgroup analysis. However, none of the other six studies included patients aged < 14 years.

Accuracy of clinical scoring tools split by primary/secondary care setting

Patients were recruited from primary care settings in five[39,44–46,52] of the six studies. Details of the primary care setting studies are outlined in *Table 10*. In brief, these studies provided point estimates of sensitivity of 0.74–0.86 and of specificity of 0.25–0.65. The single study from a secondary care setting[57] reported a higher point estimate for sensitivity (0.972, 95% CI 0.893 to 0.995) and a lower point estimate for specificity (0.172, 95% CI 0.112 to 0.253), albeit with overlapping CIs with some of the primary care setting studies, than the other five studies. This may have been a result of the setting or other sources of heterogeneity between studies.

Accuracy of clinical scoring tools using polymerase chain reaction to resolve discordant cases

No analysis of discordant results between sore throat clinical scores and microbiological culture was undertaken in any of the included studies.

Point-of-care/index tests

Accuracy of point-of-care tests with culture as the reference standard

The systematic review identified 35 pieces of literature that provided evidence comparing the performance of 18 of the named index tests with culture. These were 23 peer-reviewed papers, three abstracts, five manufacturer responses (submitted directly to NICE in response to a request for information) and four FDA reports. Two studies reported results that were inconsistent, which prevented the construction of a reliable 2 × 2 contingency table, and were excluded during the data extraction.[35,47] A summary of the final 33 pieces of literature can be found in *Table 11*. The sources provided by the manufacturers were not peer reviewed, and neither were three abstracts. The sources identified from FDA reports received some scrutiny from the FDA. The remaining 21 studies were published in peer-reviewed journals. All sensitivity and specificity estimates are presented alongside their 95% CI. Meta-analyses were performed where appropriate, a summary of which can be found in *Figure 8*.

Clearview Exact Strep A Cassette and Clearview Exact Strep A Dipstick (Abbott Laboratories)

The only evidence related to the Clearview Exact Strep A Cassette and Dipstick was provided by Andersen *et al.*,[56] who did not report which version of the test they used. Andersen *et al.*[56] reported a sensitivity of 0.68 (95% CI 0.55 to 0.81) and a specificity of 0.95 (95% CI 0.93 to 0.98) when examining children presenting in a secondary care setting.

BD Veritor Plus System (Becton Dickinson)

Azrad *et al.*[34] and Berry *et al.*[20] both presented results for the BD Veritor Plus System compared with culturing of samples in a secondary care setting. Azrad *et al.*[34] did not report the age group, and Berry *et al.*[20] looked at children. The sensitivities of the test were 0.80 (95% CI 0.59 to 0.92) and 0.76 (95% CI 0.60 to 0.87), and the specificities were 0.79 (95% CI 0.67 to 0.87) and 0.94 (95% CI 0.89 to 0.97), for Azrad *et al.*[34] and Berry *et al.*,[20] respectively. Becton Dickinson provided data to the FDA that estimated a sensitivity of 0.97 (95% CI 0.92 to 0.99) and a specificity of 0.96 (95% CI 0.94 to 0.97).[59]

Univariate models were fitted to the two studies for the BD Veritor Plus System. The models estimated a sensitivity of 0.78 (95% CI 0.67 to 0.87) and a specificity of 0.90 (95% CI 0.86 to 0.93). Heterogeneity of the studies could not be assessed using I^2 because only two studies were present.

TABLE 11 Summary of available evidence by test performance

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Clearview Exact Strep A Cassette – Abbott Laboratories											
Andersen 2003 (abstract)[56]	Secondary	Children	None	15.0	NR	353	36	17	15	285	Sensitivity 0.68 (0.55 to 0.81) Specificity 0.95 (0.93 to 0.98) PPV 0.71 (0.58 to 0.83) NPV 0.94 (0.92 to 0.97)
Clearview Exact Strep A Dipstick – Abbott Laboratories											
Andersen 2003 (abstract)[56]	Secondary	Children	None	15.0	NR	353	36	17	15	285	Sensitivity 0.68 (0.55 to 0.81) Specificity 0.95 (0.93 to 0.98) PPV 0.71 (0.58 to 0.83) NPV 0.94 (0.92 to 0.97)
BD Veritor Plus System – Becton Dickinson											
Azrad 2019[34]	Secondary	NR	None	25.0	Streptococcal selective agar	100	20	5	16	59	Sensitivity 0.80 (0.59 to 0.92) Specificity 0.79 (0.67 to 0.87) PPV 0.56 (0.38 to 0.72) NPV 0.92 (0.82 to 0.97)
[a]Becton Dickinson (FDA)[59]	NR	Children and adults	None	18.7	Blood agar	796	144	5	29	618	Sensitivity 0.97 (0.92 to 0.99) Specificity 0.96 (0.94 to 0.97) PPV 0.83 (0.77 to 0.88) NPV 0.99 (0.98 to 1.00)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Berry 2018[20]	Secondary	Children	None	19.5	Blood agar	215	32	10	11	162	Sensitivity 0.76 (0.60 to 0.87) Specificity 0.94 (0.89 to 0.97) PPV 0.74 (0.56 to 0.86) NPV 0.94 (0.89 to 0.97)
Strep A Rapid Test Cassette – Biopanda Reagents											
Biopanda Reagents (MFR)[a]	Primary	Children and adults	None	23.2	Blood agar	526	116	6	9	395	Sensitivity 0.95 (0.89 to 0.98) Specificity 0.98 (0.96 to 0.99) PPV 0.93 (0.87 to 0.96) NPV 0.99 (0.97 to 0.99)
Strep A Rapid Test Strip – Biopanda Reagents											
No data											
NADAL Strep A Strip – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
NADAL Strep A Cassette – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)

continued

TABLE 11 Summary of available evidence by test performance (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
NADAL Strep A Plus Cassette – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
NADAL Strep A Plus Strip – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
NADAL Strep A Scan – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
OSOM Strep A Strip – Sekisui Diagnostics											
Bura 2017[36]	Primary	Adults	Centor score of ≥ 2 points	22.7	Blood agar	101	22	1	2	76	Sensitivity 0.96 (0.76 to 1.00) Specificity 0.97 (0.90 to 1.00) PPV 0.92 (0.72 to 0.99) NPV 0.99 (0.92 to 1.00)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Llor 2009[44]	Primary	Adults	Centor score of ≥ 2 points	24.8	Blood agar	222	52	3	14	153	Sensitivity 0.95 (0.85 to 0.99) Specificity 0.92 (0.86 to 0.95) PPV 0.79 (0.69 to 0.86) NPV 0.98 (0.94 to 0.99)
Llor 2011[45]	Primary	Adults	Centor score of ≥ 2 points[b]	17.8	Blood agar	276	44	5	14	213	Sensitivity 0.90 (0.78 to 0.97) Specificity 0.94 (0.90 to 0.97) PPV 0.76 (0.65 to 0.84) NPV 0.98 (0.95 to 0.99)
Rogo 2011[49]	Secondary	Children	None	28.9	Blood agar	228	65	1	1	161	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.99 (0.96 to 1.00) PPV 0.98 (0.91 to 1.00) NPV 0.99 (0.96 to 1.00)
Weinzierl 2018[54]	Secondary	Children	None	38.1	Blood agar	160	54	7	9	90	Sensitivity 0.89 (0.77 to 0.95) Specificity 0.91 (0.83 to 0.96) PPV 0.86 (0.74 to 0.93) NPV 0.93 (0.85 to 0.97)
QuikRead Go Strep A Kit – Orion Diagnostica											
Azrad 2019[34]	Secondary	NR	None	25.0	Streptococcal selective agar	100	20	5	20	55	Sensitivity 0.80 (0.59 to 0.92) Specificity 0.73 (0.62 to 0.83) PPV 0.50 (0.34 to 0.66) NPV 0.92 (0.81 to 0.97)

continued

TABLE 11 Summary of available evidence by test performance (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Orion Diagnostica (MFR)[a]	Primary	Children and adults	None	32.8	Streptococcal selective agar	271	74	15	5	177	Sensitivity 0.83 (0.73 to 0.90) Specificity 0.97 (0.93 to 0.99) PPV 0.94 (0.86 to 0.97) NPV 0.92 (0.87 to 0.95)
Stefaniuk 2017[52]	Primary	Children and adults[b]	None	45.3	Blood agar	95	39	4	8	44	Sensitivity 0.91 (0.78 to 0.97) Specificity 0.85 (0.72 to 0.93) PPV 0.83 (0.72 to 0.90) NPV 0.92 (0.81 to 0.97)
Alere TestPack Plus Cassette – Abbott Laboratories											
Dimatteo 2001[38]	Secondary	Adults	Centor score of ≥ 1 point	NR	Streptococcal selective agar	NR	NR	22	NR	361	NPV 0.94 (0.91 to 0.96)
Humair 2006[39]	Primary	Adults	Centor score of ≥ 2 points[b]	37.6	Blood agar	372	128	12	11	221	Sensitivity 0.91 (0.86 to 0.95) Specificity 0.95 (0.92 to 0.98) PPV 0.92 (0.87 to 0.95) NPV 0.95 (0.91 to 0.97)
Johansson 2003[40]	Primary	Children and adults	None	31.4	NR	144	46	7	4	87	Sensitivity 0.87 (0.74 to 0.94) Specificity 0.96 (0.89 to 0.99) PPV 0.92 (0.80 to 0.97) NPV 0.93 (0.85 to 0.97)
Johnson 2001[41]	Primary	Adults	None	NR	Blood agar	NR	445	NR	77	NR	PPV 0.85 (0.82 to 0.88)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Kurtz 2000[42]	Secondary	Children	None	31.1	Blood agar	257	64	16	13	164	Sensitivity 0.80 (0.71 to 0.89) Specificity 0.93 (0.89 to 0.97) PPV 0.83 (0.75 to 0.92) NPV 0.91 (0.87 to 0.95)
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	271	87	21	623	Sensitivity 0.76 (0.71 to 0.80) Specificity 0.97 (0.95 to 0.98) PPV 0.93 (0.89 to 0.95) NPV 0.88 (0.85 to 0.90)
Lindbæk 2004[43]	Primary	Children and adults	None	35.9	Streptococcal selective agar	306	106	4	27	169	Sensitivity 0.96 (0.91 to 0.99) Specificity 0.86 (0.80 to 0.91) PPV 0.80 (0.72 to 0.86) NPV 0.98 (0.94 to 0.99)
McIsaac 2004[46]	Primary	Children and adults[b]	McIsaac score of ≥ 2 points	29.0	Blood agar	787	189	39	5	554	Sensitivity 0.83 (0.77 to 0.88) Specificity 0.99 (0.98 to 1.00) PPV 0.97 (0.94 to 0.99) NPV 0.93 (0.91 to 0.95)
Penney 2016[48]	Secondary	Children	None	40.1	Streptococcal selective agar	147	45	14	0	88	Sensitivity 0.76 (0.65 to 0.87) Specificity 1.00 (0.95 to 1.00) PPV 1.00 (0.90 to 1.00) NPV 0.86 (0.78 to 0.92)

continued

TABLE 11 Summary of available evidence by test performance (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Rosenberg 2002[50]	Secondary	Children and adults	None	25.4	Blood agar	126	24	8	1	93	Sensitivity 0.75 (0.56 to 0.88) Specificity 0.99 (0.93 to 1.00) PPV 0.96 (0.78 to 1.00) NPV 0.92 (0.85 to 0.96)
Santos 2003[51]	Secondary	Children	None	30.6	Blood agar	49	11	4	2	32	Sensitivity 0.73 (0.45 to 0.91) Specificity 0.94 (0.79 to 0.99) PPV 0.85 (0.54 to 0.97) NPV 0.89 (0.73 to 0.96)
Valverde 2018 (abstract)[58]	Secondary	Children and adults	None	40.0	Blood agar	580	181	16	27	356	Sensitivity 0.92 (0.87 to 0.95) Specificity 0.93 (0.90 to 0.95) PPV 0.87 (0.82 to 0.91) NPV 0.96 (0.93 to 0.97)
bioNexia Strep A Plus Cassette – bioMérieux											
No data											
bioNexia Strep A Dipstick – bioMérieux											
Pauchard 2013 (abstract)[57]	Secondary	Children	None	36.8	NR	193	60	11	11	111	Sensitivity 0.85 (0.74 to 0.92) Specificity 0.91 (0.84 to 0.95) PPV 0.85 (0.76 to 0.93) NPV 0.91 (0.86 to 0.96)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Biosynex Strep A Cassette											
No data											
Sofia Strep A FIA – Quidel											
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	305	53	31	613	Sensitivity 0.85 (0.81 to 0.89) Specificity 0.95 (0.93 to 0.97) PPV 0.91 (0.87 to 0.94) NPV 0.92 (0.90 to 0.94)
[a]Quidel (FDA)[60]	NR	NR	None	17.4	Blood agar	736	116	12	24	584	Sensitivity 0.91 (0.84 to 0.95) Specificity 0.96 (0.94 to 0.97) PPV 0.83 (0.75 to 0.89) NPV 0.98 (0.96 to 0.99)
Alere i Strep A – Abbott Laboratories											
Berry 2018[20]	Secondary	Children	None	19.5	Blood agar	215	42	0	15	158	Sensitivity 1.00 (0.90 to 1.00) Specificity 0.91 (0.86 to 0.95) PPV 0.74 (0.60 to 0.84) NPV 1.00 (0.97 to 1.00)
Cohen 2015[37]	Secondary	Children and adults[b]	None	30.3	Blood agar	481	141	6	18	316	Sensitivity 0.96 (0.91 to 0.98) Specificity 0.95 (0.91 to 0.97) PPV 0.89 (0.82 to 0.93) NPV 0.98 (0.96 to 0.99)

continued

TABLE 11 Summary of available evidence by test performance (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Weinzierl 2018[54]	Secondary	Children	None	38.1	Blood agar	160	60	1	0	99	Sensitivity 0.98 (0.90 to 1.00) Specificity 1.00 (0.95 to 1.00) PPV 1.00 (0.93 to 1.00) NPV 0.99 (0.94 to 1.00)
Alere i Strep A 2 – Abbott Laboratories											
[a]Abbott Laboratories (FDA)[61]	NR	NR	None	20.2	Blood agar	981	195	3	52	731	Sensitivity 0.98 (0.95 to 0.99) Specificity 0.93 (0.91 to 0.95) PPV 0.79 (0.73 to 0.84) NPV 1.00 (0.99 to 1.00)
cobas Liat Strep A Assay – Roche Diagnostics											
Roche Diagnostics (MFR)[a]	NR	Children and adults	None	30.4	Blood agar	570	170	3	23	374	Sensitivity 0.98 (0.95 to 1.00) Specificity 0.94 (0.91 to 0.96) PPV 0.88 (0.82 to 0.92) NPV 0.99 (0.97 to 1.00)
Wang 2017[24]	Primary	Children	Centor score of ≥ 1 point	30.2	NR	427	126	3	20	278	Sensitivity 0.98 (0.93 to 0.99) Specificity 0.93 (0.90 to 0.96) PPV 0.86 (0.79 to 0.91) NPV 0.99 (0.97 to 1.00)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Xpert Xpress Strep A – Cepheid											
Cepheid (MFR)[a]	NR	NR	None	23.9	NR	577	138	0	26	413	Sensitivity 1.00 (0.97 to 1.00) Specificity 0.94 (0.91 to 0.96) PPV 0.84 (0.79 to 0.89) NPV 1.00 (0.99 to 1.00)
[a]Cepheid (FDA)[62]	Primary and secondary	Children and adults	None	25.6	NR	618	157	1	27	433	Sensitivity 0.99 (0.96 to 1.00) Specificity 0.94 (0.91 to 0.96) PPV 0.85 (0.79 to 0.90) NPV 1.00 (0.99 to 1.00)

FN, false negative; FP, false positive; MFR, manufacturer; *n*, number of samples analysed; NR, not reported; TN, true negative; TP, true positive.
a The submission was provided by the company, and data were not included in the primary meta-analysis.
b Data were presented for subgroups of interest.

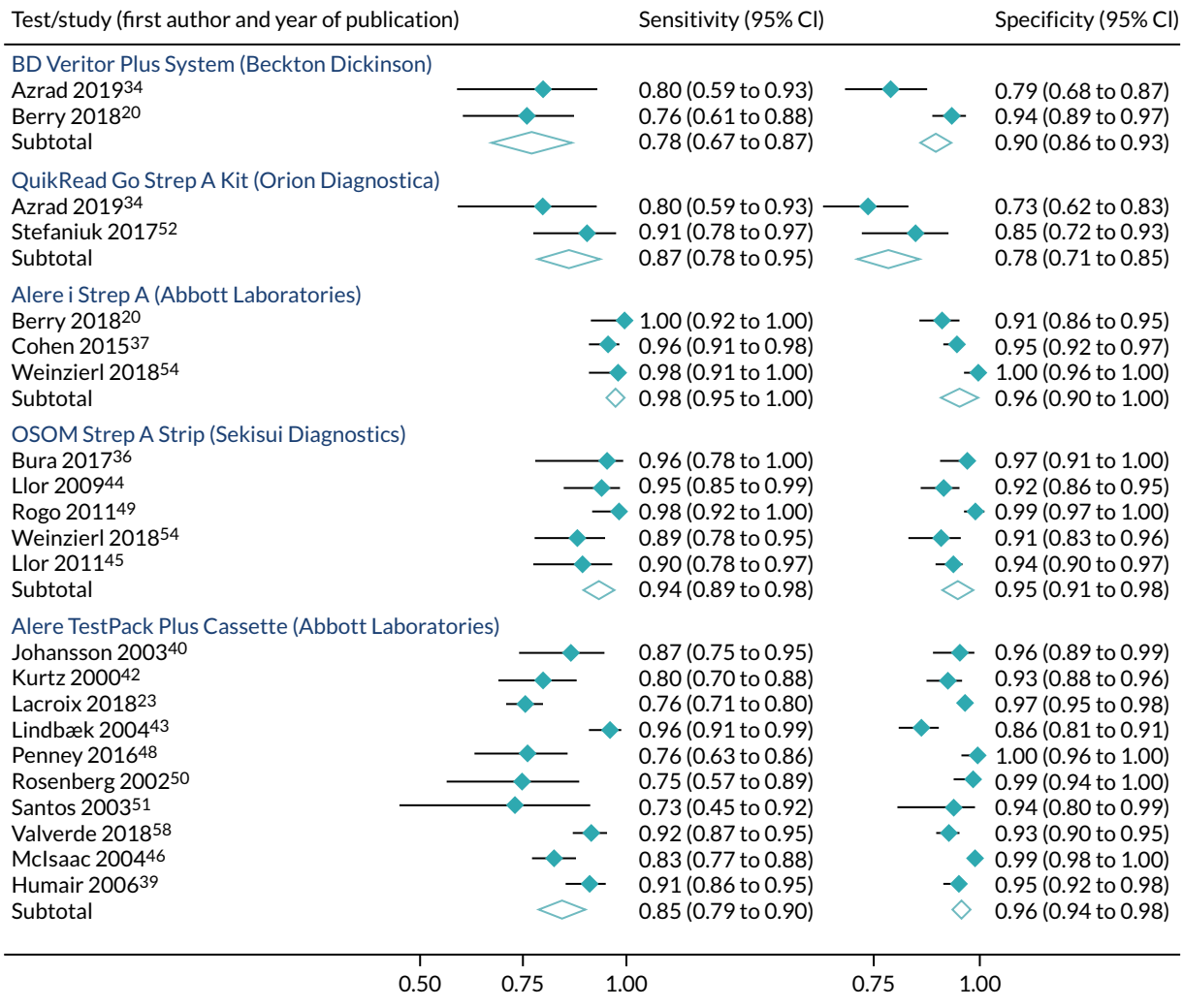

FIGURE 8 Summary of meta analyses carried out on tests with multiple studies excluding manufacturer responses and FDA reports.

Strep A Rapid Test Cassette (Biopanda Reagents)

The only evidence related to the Strep A Rapid Test Cassette was provided by Biopanda Reagents in response to a request for information by NICE. Biopanda Reagents reported a sensitivity of 0.95 (95% CI 0.89 to 0.98) and a specificity of 0.98 (95% CI 0.96 to 0.99) in a population of children and adults in a primary care setting.

NADAL Strep A Strip, NADAL Strep A Cassette, NADAL Strep A Plus Cassette, NADAL Strep A Plus Strip and NADAL Strep A Scan (nal von minden GmbH)

The only evidence related to the NADAL Strep A Cassettes, Strips and Scan tests was provided by nal von minden GmbH in response to a request for information by NICE and did not distinguish between any of the NADAL varieties. It reported a sensitivity of 0.98 (95% CI 0.91 to 1.00) and a specificity of 0.98 (95% CI 0.93 to 0.99) from a study undertaken in a secondary care setting including both children and adults.

OSOM Strep A Strip (Sekisui Diagnostics)

Five studies compared the OSOM Strep A Strip with culture.[36,44,45,49,54] Bura *et al.*,[36] Llor *et al.*[44] and Llor *et al.*[45] all examined adult populations presenting at primary care centres and reported sensitivities of 0.96 (95% CI 0.76 to 1.00), 0.95 (95% CI 0.85 to 0.99) and 0.90 (95% CI 0.78 to 0.97), and specificities of 0.97 (95% CI 0.90 to 1.00), 0.92 (95% CI 0.86 to 0.95) and 0.94 (95% CI 0.90 to 0.97), respectively.

Meanwhile Rogo *et al.*[49] and Weinzierl *et al.*[54] examined children in secondary care, with respective sensitivities of 0.98 (95% CI 0.91 to 1.00) and 0.89 (95% CI 0.77 to 0.95), and specificities of 0.99 (95% CI 0.96 to 1.00) and 0.91 (95% CI 0.83 to 0.96).

Despite having five sources of data, a bivariate model failed to converge for the OSOM test. However, univariate models did converge. These models estimated a sensitivity of 0.94 (95% CI 0.89 to 0.98) and a specificity of 0.95 (95% CI 0.91 to 0.98). The I^2 for the analysis of sensitivity was 40.65%, suggesting some heterogeneity, whereas the I^2 for the analysis of specificity was 79.14%, suggesting high heterogeneity.

QuikRead Go Strep A Kit (Orion Diagnostica)

Azrad *et al.*[34] and Stefaniuk *et al.*[52] both compared the accuracy of the QuikRead Go Strep A Kit with culture, and reported respective sensitivities of 0.80 (95% CI 0.59 to 0.92) and 0.91 (95% CI 0.78 to 0.97), and specificities of 0.73 (95% CI 0.62 to 0.83) and 0.85 (95% CI 0.72 to 0.93). Azrad *et al.*[34] investigated both child and adult patients in a primary care setting, whereas the data from Stefaniuk *et al.*[52] reflected a secondary care setting but did not report the ages of the patients. Orion Diagnostica also provided data from its own study in response to a request for information by NICE, which estimated a sensitivity of 0.83 (95% CI 0.73 to 0.90) and a specificity of 0.97 (95% CI 0.93 to 0.99) for children and adults in primary care.

Univariate models were fitted to the two studies that investigated the QuikRead Go test. The resulting sensitivity was 0.87 (95% CI 0.78 to 0.95) and the specificity was 0.78 (95% CI 0.71 to 0.85). Heterogeneity of the studies could not be assessed using I^2 because only two studies were present.

Alere TestPack Plus Cassette (Abbott Laboratories)

There were 12 published studies that compared the accuracy of the Alere TestPack Plus Cassette with culture. Two studies did not report sufficient data to estimate a complete 2 × 2 contingency table.[38,41] Four of the remaining studies were conducted in a primary care setting. One of these was in an adult population: Humair *et al.*[39] estimated a sensitivity of 0.91 (95% CI 0.86 to 0.95) and a specificity of 0.95 (95% CI 0.92 to 0.98). The other primary care-based studies combined child and adult populations: Lindbæk *et al.*[43] (sensitivity 0.94, 95% CI 0.90 to 0.99; specificity 0.86, 95% CI 0.80 to 0.91), Johansson *et al.*[40] (sensitivity 0.87, 95% CI 0.74 to 0.94; specificity 0.96, 95% CI 0.89 to 0.99) and McIsaac *et al.*[46] (sensitivity 0.83, 95% CI 0.77 to 0.88; specificity 0.99, 95% CI 0.98 to 1.00).

Six other studies were conducted in secondary care settings, three of which assessed children without any restriction from a clinical tool score.[42,48,51] Kurtz *et al.*,[42] Penney *et al.*[48] and Santos *et al.*[51] reported sensitivities of 0.80 (95% CI 0.71 to 0.89), 0.76 (95% CI 0.65 to 0.87) and 0.73 (95% CI 0.45 to 0.91), respectively. Their specificities were 0.93 (95% CI 0.89 to 0.97), 1.00 (95% CI 0.95 to 1.00) and 0.94 (95% CI 0.79 to 0.99), respectively. Lacroix *et al.*[23] also examined children in secondary care, but restricted the study population to those with a McIsaac score of $\geq$ 2 points.[23] The sensitivity was 0.76 (95% CI 0.71 to 0.80) and the specificity was 0.97 (95% CI 0.95 to 0.98). Two studies examined both children and adults in secondary care: Rosenberg *et al.*[50] estimated a sensitivity of 0.75 (95% CI 0.56 to 0.88) and a specificity of 0.99 (95% CI 0.93 to 1.00), and Valverde *et al.*[58] estimated a sensitivity of 0.92 (95% CI 0.87 to 0.95) and a specificity of 0.93 (95% CI 0.90 to 0.95).

For the Alere TestPack Plus test, a bivariate model was fitted to meta-analyse all studies. The model suggested that the test had a sensitivity of 0.85 (95% CI 0.79 to 0.90) and a specificity of 0.96 (95% CI 0.94 to 0.98). Univariate models were also investigated and were identical to two decimal places. The I^2 for the sensitivity and specificity analyses were 82.96% and 76.14%, respectively, suggesting that high heterogeneity is present in both of the meta-analyses.

bioNexia Strep A Dipstick (bioMérieux)

Only one abstract presented data for bioMérieux's bioNexia Strep A Dipstick. Pauchard *et al.*[57] conducted a study in children in a secondary care setting, and estimated a sensitivity of 0.85 (95% CI 0.74 to 0.92) and a specificity of 0.91 (95% CI 0.84 to 0.95).

Sofia Strep A fluorescent immunoassay (Quidel)

One peer-reviewed study presented data comparing the Sofia Strep A FIA with culture. Lacroix *et al.*[23] used the test on children in a secondary care setting, and estimated a sensitivity of 0.85 (95% CI 0.81 to 0.89) and a specificity of 0.95 (95% CI 0.93 to 0.97). Quidel also provided data from their own study to the FDA, which estimated a sensitivity of 0.91 (95% CI 0.84 to 0.95) and a specificity of 0.96 (95% CI 0.94 to 0.97).[60]

Alere i Strep A (Abbott Laboratories)

Three studies compared the Alere i Strep A test with culture, all in a secondary care setting. Berry *et al.*[20] and Weinzierl *et al.*[54] looked only at children, and estimated respective sensitivities of 1.00 (95% CI 0.90 to 1.00) and 0.98 (95% CI 0.90 to 1.00), and specificities of 0.91 (95% CI 0.86 to 0.95) and 1.00 (95% CI 0.95 to 1.00). Cohen *et al.*[37] examined both children and adults, and produced respective estimates of sensitivity and specificity of 0.96 (95% CI 0.91 to 0.98) and 0.95 (95% CI 0.91 to 0.97).

When meta-analysed using univariate models, the three studies using the Alere i Strep A test yielded a sensitivity of 0.98 (95% CI 0.95 to 1.00) and a specificity of 0.96 (95% CI 0.90 to 1.00). The sensitivity I^2 was 20.64% (low) and the specificity I^2 was 87.95% (high).

Alere i Strep A 2 (Abbott Laboratories)

Only manufacturer information submitted to the FDA was available for the Alere i Strep A 2 test, which reported a sensitivity of 0.98 (95% CI 0.95 to 0.99) and a specificity of 0.93 (95% CI 0.91 to 0.95), but did not report the age of patients or the care setting.[61]

cobas Liat Strep A Assay (Roche Diagnostics)

There were two sources of data comparing the cobas Liat Strep A Assay with culture. Wang *et al.*[24] carried out the test in children in a primary care setting, and estimated a sensitivity of 0.98 (95% CI 0.93 to 0.99) and a specificity of 0.94 (95% CI 0.91 to 0.96). The manufacturer (Roche Diagnostics) provided the other source in response to a request for information by NICE, which produced estimates of sensitivity and specificity of 0.98 (95% CI 0.95 to 1.00) and 0.94 (95% CI 0.91 to 0.96), respectively. Roche Diagnostics stated that the data it provided overlapped with the Wang *et al.*[24] study. The data supplied by Roche Diagnostics were identical to the data available from the FDA for this test.

Xpert Xpress Strep A (Cepheid)

Only manufacturer information was available for the Xpert Xpress Strep A test by Cepheid, which was provided in response to a request for information by NICE. The data provided by the manufacturer reported a sensitivity of 1.00 (95% CI 0.97 to 1.00) and a specificity of 0.94 (95% CI 0.91 to 0.96). This differed slightly from the information available from the FDA, which had a sensitivity of 0.99 (95% CI 0.96 to 1.00) and a specificity of 0.94 (95% CI 0.91 to 0.96).[62] Owing to the differences in sample size and the resolution of discordant samples, we have treated these sources as two independent studies, but it is not clear if there is overlap in patients.

Biosynex Strep A Cassette (Biosynex), Strep A Rapid Test Strip (Biopanda Reagents) and bioNexia Strep A Plus Cassette (bioMérieux)

No data were identified for any of the following tests:

- Biosynex Strep A Cassette test (Biosynex)
- bioNexia Strep A Plus Cassette test (bioMérieux)
- Strep A Rapid Test Strip (Biopanda Reagents).

Summary

Figures 9 and *10* present the sensitivity and specificity for all studies that had complete 2 × 2 data. Data were available for only 18 tests, and just seven tests were used in more than one independent study. Ignoring manufacturer and FDA sources of data, this reduces to 10 tests with published data and five tests with more than one independent study.

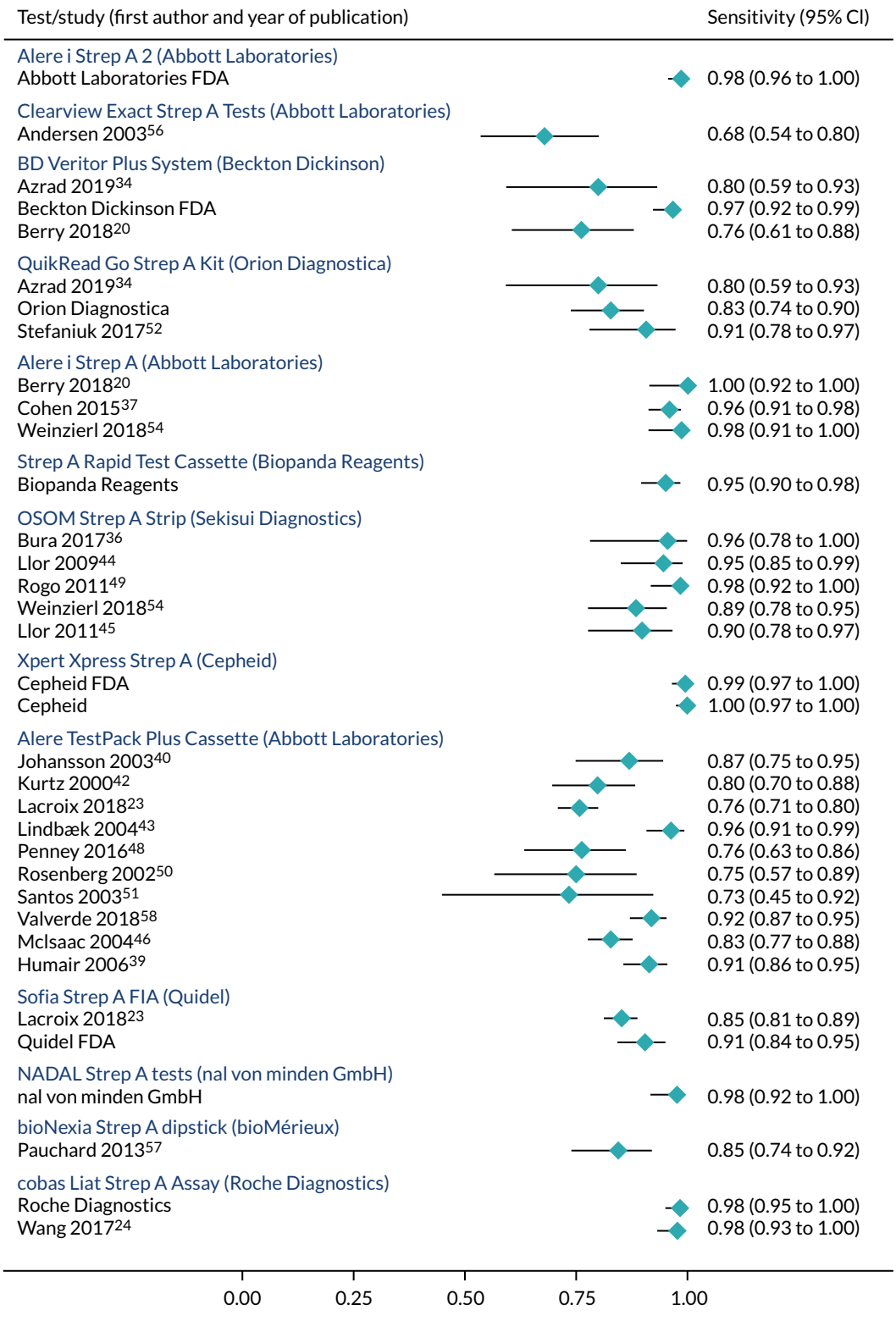

FIGURE 9 Study-level data for the studies included in the meta-analysis of test accuracy: sensitivity.

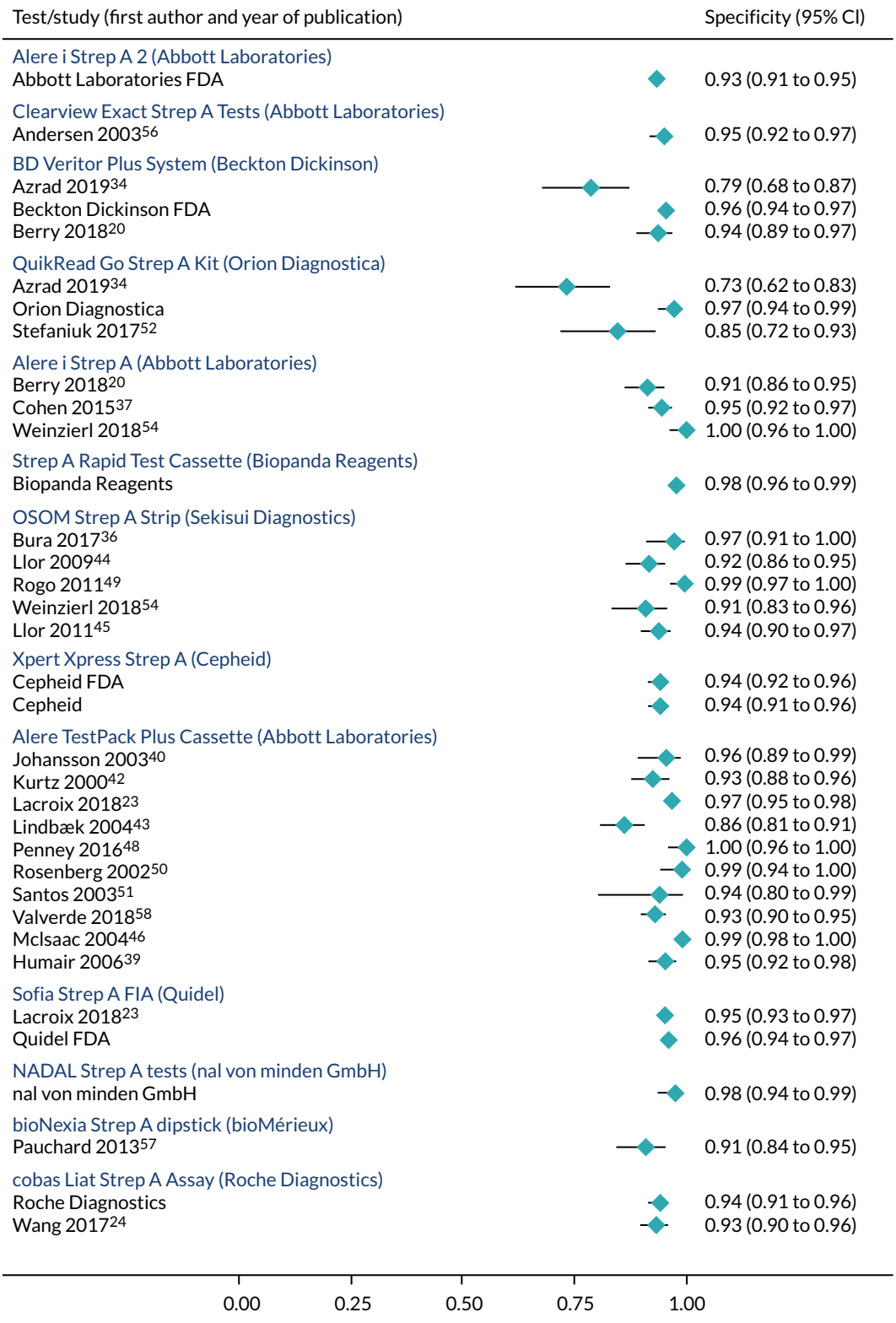

FIGURE 10 Study-level data for the studies included in the meta-analysis of test accuracy: specificity.

Note that where studies provided performance data by subgroups, these were incorporated into the relevant analyses when producing estimates to feed into the cost-effectiveness modelling. It is clear that there is a large degree of heterogeneity between the studies, and it is difficult to attribute any observed differences in test performance to the tests themselves. The CIs in *Figures 8–10* may differ slightly to those in *Table 11*, owing to differences in their method of calculation.

It is apparent that the data sourced from the manufacturer responses (submitted directly to NICE in response to a request for information) and the FDA submissions consistently provided higher estimates of sensitivity and specificity than the peer-reviewed studies. This supports the view that the manufacturer data may be judged as being at high risk of bias, and any cost-effectiveness analyses incorporating them may be unreliable.

Head-to-head (direct) comparison between tests

Initially, we sought to identify whether or not there was evidence to support the hypothesis that the tests might have different levels of accuracy. Owing to the large degree of interstudy variability, the most informative studies were those that conducted multiple tests on the same patient population, of which there were four.

Azrad *et al.*[34] compared both the BD Veritor System (Becton Dickinson) and the QuikRead Go Strep A Kit (Orion Diagnostica) with culture for 100 patients. The BD Veritor System had a sensitivity of 0.80 (95% CI 0.59 to 0.92) and a specificity of 0.79 (95% CI 0.67 to 0.87). The QuikRead Go test had an identical sensitivity, of 0.80 (95% CI 0.59 to 0.92), and a slightly lower point estimate for specificity, of 0.73, with overlapping CIs (95% CI 0.62 to 0.83).

Berry *et al.*[20] compared both the BD Veritor System and the Alere i Strep A tests with culture. The tests performed differently, with the BD Veritor System having a sensitivity of 0.76 (95% CI 0.60 to 0.87) and a specificity of 0.94 (95% CI 0.89 to 0.97) and Alere i Strep A having a sensitivity of 1.00 (95% CI 0.90 to 1.00) and a specificity of 0.91 (95% CI 0.86 to 0.95).

Lacroix *et al.*[23] investigated both the Alere TestPack Plus and the Sofia Strep A FIA tests. Again, the tests performed differently, with the Alere TestPack Plus having lower detection rates, with a sensitivity of 0.76 (95% CI 0.71 to 0.80) and a specificity of 0.97 (95% CI 0.95 to 0.98). Meanwhile, the Sofia Strep A FIA had a sensitivity of 0.85 (95% CI 0.81 to 0.89) and a specificity of 0.95 (95% CI 0.93 to 0.97).

Finally, Weinzierl *et al.*[54] assessed the Alere i Strep A and the OSOM Strep A Strip tests. The OSOM Strep A Strip had a sensitivity of 0.89 (95% CI 0.77 to 0.95) and a specificity of 0.91 (95% CI 0.83 to 0.96), whereas the Alere i Strep A test had a sensitivity of 0.98 (95% CI 0.90 to 1.00) and a specificity of 1.00 (95% CI 0.95 to 1.00).

Conclusion

There is insufficient evidence to conduct a meaningful comparison of the rapid tests or to establish any reliable hierarchy of test performance. Although some tests may perform similarly, the existing evidence does not allow identification of any clear groups of tests, and it is likely that there is some variation in accuracy of the 21 tests. There is considerable heterogeneity, potentially caused by the differences in study design and population.

Accuracy of point-of-care tests in the population at high risk of group A *Streptococcus* infection as defined by sore throat clinical scores

The primary population of interest in this review is patients with high clinical scores (Centor score of ≥ 3 points, FeverPAIN score of ≥ 4 points). We report test accuracy data in that population, and for other thresholds of clinical measuring tools, such as Centor or McIsaac, as were reported by published studies. The majority of studies either did not place or did not report placing a restriction of the clinical scoring tool on their patient populations.

Eight studies present results based on some restriction of Centor or McIsaac (either ≥ 1 point or 2 or 3 points), which informed test accuracy data for four tests. A summary of evidence is provided in *Table 12*.

TABLE 12 Summary of data informing test performance in studies that restricted their population by clinical throat score

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
OSOM Strep A Strip – Sekisui Diagnostics											
Bura 2017[36]	Primary	Adults	Centor score of ≥ 2 points	22.7	Blood agar	101	22	1	2	76	Sensitivity 0.96 (0.76 to 1.00) Specificity 0.97 (0.90 to 1.00) PPV 0.92 (0.72 to 0.99) NPV 0.99 (0.92 to 1.00)
Llor 2009[44]	Primary	Adults	Centor score of ≥ 2 points	24.8	Blood agar	222	52	3	14	153	Sensitivity 0.95 (0.85 to 0.99) Specificity 0.92 (0.86 to 0.95) PPV 0.79 (0.69 to 0.86) NPV 0.98 (0.94 to 0.99)
Llor 2011[45]	Primary	Adults	Centor score of ≥ 1 point	17.8	Blood agar	276	44	5	14	213	Sensitivity 0.90 (0.78 to 0.97) Specificity 0.94 (0.90 to 0.97) PPV 0.76 (0.65 to 0.84) NPV 0.98 (0.95 to 0.99)
Llor 2011[45]	Primary	Adults	Centor score of > 2 points	31.0	Blood agar	116	33	3	3	77	Sensitivity 0.92 (0.76 to 0.98) Specificity 0.96 (0.89 to 0.99) PPV 0.92 (0.78 to 0.97) NPV 0.96 (0.90 to 0.99)
Llor 2011[45]	Primary	Adults	Centor score of = 1 or 2 points	8.1	Blood agar	160	11	2	11	136	Sensitivity 0.85 (0.55 to 0.98) Specificity 0.93 (0.87 to 0.96) PPV 0.50 (0.35 to 0.65) NPV 0.99 (0.95 to 1.00)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Alere TestPack Plus Cassette – Abbott Laboratories											
Dimatteo 2001[38]	Secondary	Adults	Centor score of ≥ 1 point	NR	Streptococcal selective agar			22		361	NPV 0.94 (0.91 to 0.96)
Humair 2006[39]	Primary	Adults	Centor score of ≥ 2 points	37.6	Blood agar	372	128	12	11	221	Sensitivity 0.91 (0.86 to 0.95) Specificity 0.95 (0.92 to 0.98) PPV 0.92 (0.87 to 0.95) NPV 0.95 (0.91 to 0.97)
Humair 2006[39]	Primary	Adults	Centor score of = 2 points	23.6	Blood agar	148	28	7	4	109	Sensitivity 0.80 (0.63 to 0.92) Specificity 0.96 (0.91 to 0.99) PPV 0.88 (0.73 to 0.95) NPV 0.94 (0.89 to 0.97)
Humair 2006[39]	Primary	Adults	Centor score of > 2 points	46.9	Blood agar	224	100	5	7	112	Sensitivity 0.95 (0.89 to 0.98) Specificity 0.94 (0.88 to 0.98) PPV 0.93 (0.87 to 0.97) NPV 0.96 (0.90 to 0.98)
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	271	87	21	623	Sensitivity 0.76 (0.71 to 0.80) Specificity 0.97 (0.95 to 0.98) PPV 0.93 (0.89 to 0.95) NPV 0.88 (0.85 to 0.90)

continued

TABLE 12 Summary of data informing test performance in studies that restricted their population by clinical throat score (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
McIsaac 2004[46]	Primary	Children and adults[a]	McIsaac score of ≥ 2 points	29.0	Blood agar	787	189	39	5	554	Sensitivity 0.83 (0.77 to 0.88) Specificity 0.99 (0.98 to 1.00) PPV 0.97 (0.94 to 0.99) NPV 0.93 (0.91 to 0.95)
Sofia Strep A FIA – Quidel											
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	305	53	31	613	Sensitivity 0.85 (0.81 to 0.89) Specificity 0.95 (0.93 to 0.97) PPV 0.91 (0.87 to 0.94) NPV 0.92 (0.90 to 0.94)
cobas Liat Strep A Assay – Roche Diagnostics											
Wang 2017[24]	Primary	Children	Centor score of ≥ 1 point	30.2	NR	427	126	3	20	278	Sensitivity 0.98 (0.93 to 0.99) Specificity 0.93 (0.90 to 0.96) PPV 0.86 (0.79 to 0.91) NPV 0.99 (0.97 to 1.00)

FN, false negative; FP, false positive; NR, not reported; TN, true negative; TP, true positive.
a Data were presented for subgroups of interest.

Only two studies presented data for populations that matched the NICE scope, that is having either a Centor or McIsaac score of ≥ 3 points or a FeverPAIN score of ≥ 4 points.[39,45] We dichotomised the data from these studies into (1) patients meeting the scope based on throat score and (2) patients not meeting the scope.

Humair *et al.*[39] investigated the Alere TestPack Plus test in adults presenting in a primary care setting, with a Centor score of ≥ 2 points. In the Centor score = 2 points and Centor score of > 2 points subgroups, the sensitivities were 0.80 (95% CI 0.63 to 0.92) and 0.95 (95% CI 0.89 to 0.98), and the specificities were 0.96 (95% CI 0.91 to 0.99) and 0.94 (95% CI 0.88 to 0.98), respectively. The subgroups had 148 and 224 patients, respectively.

Llor *et al.*[45] investigated adult patients in a primary care setting with a Centor score of ≥ 1 point when assessing the performance of the OSOM Strep A Strip. In the population with a Centor score of 1 or 2 points, consisting of 160 patients, the OSOM Strep A Strip had a sensitivity of 0.85 (95% CI 0.55 to 0.98) and a specificity of 0.93 (95% CI 0.87 to 0.96). In the population with a Centor score of > 2 points, with 116 patients, the test had a sensitivity of 0.92 (95% CI 0.76 to 0.98) and a specificity of 0.96 (95% CI 0.89 to 0.99).

The remaining data for studies that restricted their populations by throat score are presented in the following sections.

OSOM Strep A Strip

Three studies compared the OSOM Strep A Strip in a restricted population. Bura *et al.*[36] and Llor *et al.*[44] both focused on patients with a Centor score of ≥ 2 points, and reported sensitivities of 0.96 (95% CI 0.76 to 1.00) and 0.95 (95% CI 0.85 to 0.99), and specificities of 0.97 (95% CI 0.90 to 1.00) and 0.92 (95% CI 0.86 to 0.95), respectively.

Meanwhile Llor *et al.*[45] considered patients with a Centor score of ≥ 1 point and reported a sensitivity of 0.90 (95% CI 0.78 to 0.97) and a specificity of 0.94 (95% CI 0.90 to 0.97).

Alere TestPack Plus Cassette

Four studies investigating the Alere TestPack Plus restricted their population by throat score. Dimatteo *et al.*[38] looked only at patients with a Centor score of ≥ 1 point but did not present complete 2 × 2 information and so sensitivity and specificity could not be calculated. Lacroix *et al.*[23] and McIsaac *et al.*[46] both examined test performance in patients with McIsaac scores of ≥ 2 points. The former estimated a sensitivity of 0.76 (95% CI 0.71 to 0.80) and a specificity of 0.97 (95% CI 0.95 to 0.98), and the latter estimated a sensitivity of 0.83 (95% CI 0.77 to 0.88) and a specificity of 0.99 (95% CI 0.98 to 1.00).

Humair *et al.*[39] also considered only patients with a Centor score of ≥ 2 points, but also presented results by score subgroup mentioned in *Accuracy of point-of-care tests in the population at high risk of group A* Streptococcus *infection as defined by sore throat clinical scores*. In the full population, a sensitivity of 0.91 (95% CI 0.86 to 0.95) and a specificity of 0.95 (95% CI 0.92 to 0.98) were reported.

Sofia Strep A fluorescent immunoassay

One study compared Sofia Strep A FIA with culture and restricted the population by throat score. Lacroix *et al.*[23] used Sofia Strep A FIA in patients with a McIsaac score of ≥ 2 points. In this population, the test had a sensitivity of 0.85 (95% CI 0.81 to 0.89) and a specificity of 0.95 (95% CI 0.93 to 0.97).

cobas Liat Strep A Assay

One study compared cobas Liat Strep A Assay with culture in patients restricted by throat score. Wang *et al.*[24] used the test in patients with a Centor score of ≥ 1 point. In this population, the test had a sensitivity of 0.98 (95% CI 0.93 to 0.99) and a specificity of 0.93 (95% CI 0.90 to 0.96).

Conclusion

The limited evidence suggests that some tests may have a higher sensitivity in patient populations that have a higher score according to a clinical tool, such as Centor.

Accuracy of point-of-care tests split by age group

We sought to identify whether or not there was evidence to support the hypothesis that the tests might have different performance characteristics based on the age group on which the test is being used. No studies were categorised into the age groups as detailed in the NICE scope, and so we classified them into child and adult populations where possible, or a combination of children and adults. No studies presented results specific to a ≥ 60-year-old population, although patients in this category may have been included within an 'adult' population. Seven studies concentrated on exclusively adult populations, providing accuracy data for two tests.[36,38,39,41,43–45] Ten studies looked exclusively at children, providing data for nine tests.[20,23,24,42,48,49,51,54,56,57] Three studies considered both adults and children, and presented accuracy data for them separately, allowing a within-trial comparison to be made.[37,46,52] Each of these three studies investigated a different test.

Cohen *et al.*[37] examined both adults and children when investigating the accuracy of the Alere i Strep A test. In children, the test had a sensitivity of 0.96 (95% CI 0.91 to 0.99) and a specificity of 0.93 (95% CI 0.89 to 0.96). In adults, the sensitivity was 0.95 (95% CI 0.74 to 1.00) and the specificity was 0.97 (95% CI 0.92 to 0.99).

McIsaac *et al.*[46] examined the Alere TestPack Plus test in child and adult populations, presenting the results by age category. In children, the sensitivity was 0.86 (95% CI 0.79 to 0.91) and the specificity was 0.99 (95% CI 0.97 to 1.00). In adults, the sensitivity was 0.77 (95% CI 0.65 to 0.86) and the specificity was 0.99 (95% CI 0.97 to 1.00).

Stefaniuk *et al.*[52] used the QuikRead Go Strep A Kit test in both adults and children. In children, a sensitivity of 0.80 (95% CI 0.56 to 0.94) and a specificity of 0.91 (95% CI 0.72 to 0.99) were estimated. In adults, the test sensitivity was 1.00 (95% CI 0.86 to 0.95) and specificity was 0.79 (95% CI 0.60 to 0.92).

Further age-specific results are presented below and in *Table 13*.

Clearview Exact Strep A Cassette and Clearview Exact Strep A Dipstick (Abbott Laboratories)

Only data for a child population were available for the Clearview Exact Strep A Cassette and Dipstick tests, and were provided by Andersen *et al.*,[56] who did not distinguish between the cassette and dipstick varieties. Andersen *et al.*[56] reported a sensitivity of 0.68 (95% CI 0.55 to 0.81) and a specificity of 0.95 (95% CI 0.93 to 0.98).

BD Veritor Plus System (Becton Dickinson)

The only age-specific test accuracy data for the BD Veritor Plus System were in children, and published by Berry *et al.*[20] The sensitivity of the test was 0.76 (95% CI 0.60 to 0.87) and the specificity was 0.94 (95% CI 0.89 to 0.97).

OSOM Strep A Strip (Sekisui Diagnostics)

Three studies presented data for the OSOM Strep A Strip in adult patients.[36,44,45] Bura *et al.*,[36] Llor *et al.*[44] and Llor *et al.*[45] reported respective sensitivities of 0.96 (95% CI 0.76 to 1.00), 0.95 (95% CI 0.85 to 0.99) and 0.90 (95% CI 0.78 to 0.97), and specificities of 0.97 (95% CI 0.90 to 1.00), 0.92 (95% CI 0.86 to 0.95) and 0.94 (95% CI 0.90 to 0.97). Rogo *et al.*[49] and Weinzierl *et al.*[54] both studied children only, and estimated sensitivities of 0.98 (95% CI 0.91 to 1.00) and 0.89 (95% CI 0.77 to 0.95), and specificities of 0.99 (95% CI 0.96 to 1.00) and 0.91 (95% CI 0.83 to 0.96), respectively.

TABLE 13 Summary of test data for age groups of interest

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Clearview Exact Strep A Cassette – Abbott Laboratories											
Andersen 2003[56]	Secondary	Children	None	15.0	NR	353	36	17	15	285	Sensitivity 0.68 (0.55 to 0.81) Specificity 0.95 (0.93 to 0.98) PPV 0.71 (0.58 to 0.83) NPV 0.94 (0.92 to 0.97)
Clearview Exact Strep A Dipstick – Abbott Laboratories											
Andersen 2003[56]	Secondary	Children	None	15.0	NR	353	36	17	15	285	Sensitivity 0.68 (0.55 to 0.81) Specificity 0.95 (0.93 to 0.98) PPV 0.71 (0.58 to 0.83) NPV 0.94 (0.92 to 0.97)
BD Veritor Plus System – Becton Dickinson											
Berry 2018[20]	Secondary	Children	None	19.5	Blood agar	215	32	10	11	162	Sensitivity 0.76 (0.60 to 0.87) Specificity 0.94 (0.89 to 0.97) PPV 0.74 (0.56 to 0.86) NPV 0.94 (0.89 to 0.97)
OSOM Strep A Strip – Sekisui Diagnostics											
Bura 2017[36]	Primary	Adults	Centor score of ≥ 2 points	22.7	Blood agar	101	22	1	2	76	Sensitivity 0.96 (0.76 to 1.00) Specificity 0.97 (0.90 to 1.00) PPV 0.92 (0.72 to 0.99) NPV 0.99 (0.92 to 1.00)

continued

TABLE 13 Summary of test data for age groups of interest (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Llor 2009[44]	Primary	Adults	Centor score of ≥ 2 points	24.8	Blood agar	222	52	3	14	153	Sensitivity 0.95 (0.85 to 0.99) Specificity 0.92 (0.86 to 0.95) PPV 0.79 (0.69 to 0.86) NPV 0.98 (0.94 to 0.99)
Llor 2011[45]	Primary	Adults	Centor score of ≥ 2 points[a]	17.8	Blood agar	276	44	5	14	213	Sensitivity 0.90 (0.78 to 0.97) Specificity 0.94 (0.90 to 0.97) PPV 0.76 (0.65 to 0.84) NPV 0.98 (0.95 to 0.99)
Rogo 2011[49]	Secondary	Children	None	28.9	Blood agar	228	65	1	1	161	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.99 (0.96 to 1.00) PPV 0.98 (0.91 to 1.00) NPV 0.99 (0.96 to 1.00)
Weinzierl 2018[54]	Secondary	Children	None	38.1	Blood agar	160	54	7	9	90	Sensitivity 0.89 (0.77 to 0.95) Specificity 0.91 (0.83 to 0.96) PPV 0.86 (0.74 to 0.93) NPV 0.93 (0.85 to 0.97)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
QuikRead Go Strep A Kit – Orion Diagnostica											
Stefaniuk 2017[52]	Primary	Children	None	46.5	Blood agar	43	16	4	2	21	Sensitivity 0.80 (0.56 to 0.94) Specificity 0.91 (0.72 to 0.99) PPV 0.89 (0.68 to 0.97) NPV 0.84 (0.68 to 0.93)
Stefaniuk 2017[52]	Primary	Adults	None	44.2	Blood agar	52	23	0	6	23	Sensitivity 1.00 (0.85 to 1.00) Specificity 0.79 (0.60 to 0.92) PPV 0.79 (0.65 to 0.89) NPV 1.00 (0.85 to 1.00)
Alere TestPack Plus Cassette – Abbott Laboratories											
Dimatteo 2001[38]	Secondary	Adults	Centor score of ≥ 1 point	NR	Streptococcal selective agar			22		361	NPV 0.94 (0.91 to 0.96)
Humair 2006[39]	Primary	Adults	Centor score of ≥ 2 points[a]	37.6	Blood agar	372	128	12	11	221	Sensitivity 0.91 (0.86 to 0.95) Specificity 0.95 (0.92 to 0.98) PPV 0.92 (0.87 to 0.95) NPV 0.95 (0.91 to 0.97)
Johnson 2001[41]	Primary	Adults	None	NR	Blood agar		445		77		PPV 0.85 (0.82 to 0.88)
Kurtz 2000[42]	Secondary	Children	None	31.1	Blood agar	257	64	16	13	164	Sensitivity 0.80 (0.71 to 0.89) Specificity 0.93 (0.89 to 0.97) PPV 0.83 (0.75 to 0.92) NPV 0.91 (0.87 to 0.95)

continued

TABLE 13 Summary of test data for age groups of interest (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	271	87	21	623	Sensitivity 0.76 (0.71 to 0.80) Specificity 0.97 (0.95 to 0.98) PPV 0.93 (0.89 to 0.95) NPV 0.88 (0.85 to 0.90)
McIsaac 2004[46]	Primary	Children	McIsaac score of ≥ 2 points	34.1	Blood agar	454	133	22	3	296	Sensitivity 0.86 (0.79 to 0.91) Specificity 0.99 (0.97 to 1.00) PPV 0.98 (0.93 to 0.99) NPV 0.93 (0.90 to 0.95)
McIsaac 2004[46]	Primary	Adults	McIsaac score of ≥ 2 points	21.9	Blood agar	333	56	17	2	258	Sensitivity 0.77 (0.65 to 0.86) Specificity 0.99 (0.97 to 1.00) PPV 0.97 (0.88 to 0.99) NPV 0.94 (0.91 to 0.96)
Penney 2016[48]	Secondary	Children	None	40.1	Streptococcal selective agar	147	45	14	0	88	Sensitivity 0.76 (0.65 to 0.87) Specificity 1.00 (0.95 to 1.00) PPV 1.00 (0.90 to 1.00) NPV 0.86 (0.78 to 0.92)
Santos 2003[51]	Secondary	Children	None	30.6	Blood agar	49	11	4	2	32	Sensitivity 0.73 (0.45 to 0.91) Specificity 0.94 (0.79 to 0.99) PPV 0.85 (0.54 to 0.97) NPV 0.89 (0.73 to 0.96)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
bioNexia Strep A Dipstick – bioMérieux											
Pauchard 2013[57]	Secondary	Children	None	36.8	NR	193	60	11	11	111	Sensitivity 0.85 (0.74 to 0.92) Specificity 0.91 (0.84 to 0.95) PPV 0.85 (0.76 to 0.93) NPV 0.91 (0.86 to 0.96)
Sofia Strep A FIA – Quidel											
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	305	53	31	613	Sensitivity 0.85 (0.81 to 0.89) Specificity 0.95 (0.93 to 0.97) PPV 0.91 (0.87 to 0.94) NPV 0.92 (0.90 to 0.94)
Alere i Strep A – Abbott Laboratories											
Berry 2018[20]	Secondary	Children	None	19.5	Blood agar	215	42	0	15	158	Sensitivity 1.00 (0.90 to 1.00) Specificity 0.91 (0.86 to 0.95) PPV 0.74 (0.60 to 0.84) NPV 1.00 (0.97 to 1.00)
Cohen 2015[37]	Secondary	Children	None		Blood agar	355	123	5	15	212	Sensitivity 0.96 (0.91 to 0.99) Specificity 0.93 (0.89 to 0.96) PPV 0.89 (0.83 to 0.93) NPV 0.98 (0.95 to 0.99)

continued

TABLE 13 Summary of test data for age groups of interest (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Cohen 2015[37]	Secondary	Adults	None		Blood agar	126	18	1	3	104	Sensitivity 0.95 (0.74 to 1.00) Specificity 0.97 (0.92 to 0.99) PPV 0.86 (0.66 to 0.95) NPV 0.99 (0.94 to 1.00)
Weinzierl 2018[54]	Secondary	Children	None	38.1	Blood agar	160	60	1	0	99	Sensitivity 0.98 (0.90 to 1.00) Specificity 1.00 (0.95 to 1.00) PPV 1.00 (0.93 to 1.00) NPV 0.99 (0.94 to 1.00)
cobas Liat Strep A Assay – Roche Diagnostics											
Wang 2017[24]	Primary	Children	Centor score of ≥ 1 point	30.2	NR	427	126	3	20	278	Sensitivity 0.98 (0.93 to 0.99) Specificity 0.93 (0.90 to 0.96) PPV 0.86 (0.79 to 0.91) NPV 0.99 (0.97 to 1.00)

FN, false negative; FP, false positive; NR, not reported; TN, true negative; TP, true positive.
a Data were presented for subgroups of interest.

QuikRead Go Strep A Kit (Orion Diagnostica)

Stefaniuk *et al.*[52] examined both adults and children. In children, a sensitivity of 0.80 (95% CI 0.56 to 0.94) and a specificity of 0.91 (95% CI 0.72 to 0.99) were estimated. In adults, the test sensitivity was 1.00 (95% CI 0.85 to 1.00) and the specificity was 0.79 (95% CI 0.60. 0.92).

Alere TestPack Plus (Abbott Laboratories)

Three studies used the Alere TestPack Plus test in adult populations.[38,39,41] Dimatteo *et al.*[38] and Johnson *et al.*[41] did not provide complete results, and sensitivity and specificity could not be calculated. Humair *et al.*[39] did provide sufficient information and the test's sensitivity was 0.91 (95% CI 0.86 to 0.95). The specificity was 0.95 (95% CI 0.92 to 0.98).

Four studies used the test in child populations only.[23,42,48,51] The lowest sensitivity was reported by Santos *et al.*[51] (0.73, 95% CI 0.45 to 0.91) and the highest by Kurtz *et al.*[42] (0.80, 95% CI 0.71 to 0.89). The sensitivities ranged from 0.93 (95% CI 0.89 to 0.97), as reported by Kurtz *et al.*,[42] to 1.00 (95% CI 0.95 to 1.00), as reported by Penney *et al.*[48] McIsaac *et al.*[46] conducted the test in both groups. In children, the sensitivity was 0.86 (95% CI 0.79 to 0.91) and the specificity was 0.99 (95% CI 0.97 to 1.00). In adults, the sensitivity was 0.77 (95% CI 0.65 to 0.86), with a specificity of 0.99 (95% CI 0.97 to 1.00).

bioNexia Strep A Dipstick (bioMérieux)

Only data for children were available for bioMérieux's bioNexia Strep A Dipstick. Pauchard *et al.*[57] estimated a sensitivity of 0.85 (95% CI 0.74 to 0.92) and a specificity of 0.91 (95% CI 0.84 to 0.95).

Sofia Strep A fluorescent immunoassay (Quidel)

One study compared Sofia Strep A FIA with culture in children, with no adult data available. Lacroix *et al.*[23] reported a sensitivity of 0.85 (95% CI 0.81 to 0.89) and a specificity of 0.95 (95% CI 0.93 to 0.97).

Alere i Strep A (Abbott Laboratories)

Two studies presented data for the Alere i Strep A test for child populations.[20,54] Berry *et al.*[20] and Weinzierl *et al.*[54] reported respective sensitivities of 1.00 (95% CI 0.90 to 1.00) and 0.98 (95% CI 0.90 to 1.00), and specificities of 0.91 (95% CI 0.86 to 0.95) and 1.00 (95% CI 0.95 to 1.00).

Cohen *et al.*[37] examined both adults and children, and presented results by age group. In children, the test had a sensitivity of 0.96 (95% CI 0.91 to 0.99) and a specificity of 0.93 (95% CI 0.89 to 0.96). In adults, the sensitivity was 0.95 (95% CI 0.74 to 1.00) and the specificity was 0.97 (95% CI 0.92 to 0.99).

cobas Liat Strep A Assay (Roche Diagnostics)

Only data for a child population were available for the cobas Liat Strep A Assay. Wang *et al.*[24] reported that the test had a sensitivity of 0.98 (95% CI 0.93 to 0.99) and a specificity of 0.93 (95% CI 0.90 to 0.96).

Meta-analyses were carried out to compare the accuracy estimates of the child and adult populations for both the OSOM Strep A Strip and the Alere TestPack Plus tests, as these were the only tests with sufficient data.

For the TestPack Plus, in children, the sensitivity was estimated as 0.80 (95% CI 0.74 to 0.84) and the specificity as 0.98 (95% CI 0.95 to 0.99). In adults, the sensitivity was estimated as 0.87 (95% CI 0.82 to 0.91) and the specificity as 0.98 (95% CI 0.96 to 0.99).

For OSOM, the dichotomisation of studies into the two age categories was identical to the dichotomisation for primary and secondary care settings. Univariate models fitted to the children/secondary care data estimated a sensitivity of 0.95 (95% CI 0.90 to 0.98) and a specificity of 0.97 (95% CI 0.95 to 0.99). Models fitted to the adult/primary care data estimated a sensitivity of 0.93 (95% CI 0.88 to 0.97) and a specificity of 0.94 (95% CI 0.91 to 0.97).

Conclusion

It is unclear whether or not test accuracy varies based on the age of the population in which the test is being used. Further evidence is required.

Accuracy of point-of-care tests split by primary/secondary care setting

We sought to identify whether or not there was evidence to support the hypothesis that the tests might have different performance characteristics based on the setting in which the test is being used. No studies provided a breakdown of results comparing test accuracy between primary and secondary settings. Fourteen studies considered patients in a secondary care setting, which provided data for nine tests. Ten studies looked at patients in primary care settings, which covered four tests. A summary of care-setting-related data can be found in *Table 14*.

Clearview Exact Strep A Cassette and Clearview Exact Strep A Dipstick (Abbott Laboratories)

Only data in a hospital setting were available for the Clearview Exact Strep A Cassette and Dipstick tests, and were provided by Andersen *et al.*,[56] who did not distinguish between the cassette and the dipstick varieties. Andersen *et al.*[56] reported a sensitivity of 0.68 (95% CI 0.55 to 0.81) and a specificity of 0.95 (95% CI 0.93 to 0.98).

BD Veritor Plus System (Becton Dickinson)

Azrad *et al.*[34] and Berry *et al.*[20] both presented results for the BD Veritor Plus System in a hospital setting. The sensitivities of the test were 0.80 (95% CI 0.59 to 0.92) and 0.76 (95% CI 0.60 to 0.87), and the specificities were 0.79 (95% CI 0.67 to 0.87) and 0.94 (95% CI 0.89 to 0.97), for Azrad *et al.*[34] and Berry *et al.*,[20] respectively.

NADAL Strep A Strip, NADAL Strep A Cassette, NADAL Strep A Plus Cassette, NADAL Strep A Plus Strip and NADAL Strep A Scan (nal von minden GmbH)

Only evidence from a secondary care setting was available for the NADAL tests, which did not distinguish between any of the varieties. The manufacturer reported a sensitivity of 0.98 (95% CI 0.91 to 1.00) and a specificity of 0.98 (95% CI 0.93 to 0.99).

Strep A Rapid Test Cassette (Biopanda Reagents)

The data provided by Biopanda Reagents for the Strep A Rapid Test were reportedly from a primary care setting. The sensitivity was 0.95 (95% CI 0.0.89 to 0.98) and the specificity was 0.98 (95% CI 0.96 to 0.99).

OSOM Strep A Strip (Sekisui Diagnostics)

Three studies presented data for the OSOM Strep A Strip in a primary care setting.[36,44,45] Bura *et al.*,[36] Llor *et al.*[44] and Llor *et al.*[45] reported respective sensitivities of 0.96 (95% CI 0.76 to 1.00), 0.95 (95% CI 0.85 to 0.99) and 0.90 (95% CI 0.78 to 0.97), and specificities of 0.97 (95% CI 0.90 to 1.00), 0.92 (95% CI 0.86 to 0.95) and 0.94 (95% CI 0.90 to 0.97). Rogo *et al.*[49] and Weinzierl *et al.*[54] both used the test in a hospital setting, and estimated sensitivities of 0.98 (95% CI 0.91 to 1.00) and 0.89 (95% CI 0.77 to 0.95), and specificities of 0.99 (95% CI 0.96 to 1.00) and 0.91 (95% CI 0.83 to 0.96), respectively.[49,54]

QuikRead Go Strep A Kit (Orion Diagnostica)

Azrad *et al.*[34] compared the performance of the QuikRead Go Strep A Kit with culture in a hospital setting, and reported a sensitivity of 0.80 (95% CI 0.59 to 0.92) and a specificity of 0.73 (95% CI 0.62 to 0.83). Stefaniuk *et al.*[52] looked at a primary care setting, and reported a sensitivity 0.91 (95% CI 0.78 to 0.97) and a specificity 0.85 (95% CI 0.72 to 0.93). The data provided by Orion Diagnostica were also reported as being from a primary care setting, and estimated a sensitivity of 0.83 (95% CI 0.73 to 0.90) and a specificity of 0.97 (95% CI 0.93 to 0.99).

TABLE 14 Summary of test performance data by care setting

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Clearview Exact Strep A Cassette – Abbott Laboratories											
Andersen 2003[56]	Secondary	Children	None	15.0	NR	353	36	17	15	285	Sensitivity 0.68 (0.55 to 0.81) Specificity 0.95 (0.93 to 0.98) PPV 0.71 (0.58 to 0.83) NPV 0.94 (0.92 to 0.97)
Clearview Exact Strep A Dipstick – Abbott Laboratories											
Andersen 2003[56]	Secondary	Children	None	15.0	NR	353	36	17	15	285	Sensitivity 0.68 (0.55 to 0.81) Specificity 0.95 (0.93 to 0.98) PPV 0.71 (0.58 to 0.83) NPV 0.94 (0.92 to 0.97)
BD Veritor Plus System – Becton Dickinson											
Azrad 2019[34]	Secondary	NR	None	25.0	Streptococcal selective agar	100	20	5	16	59	Sensitivity 0.80 (0.59 to 0.92) Specificity 0.79 (0.67 to 0.87) PPV 0.56 (0.38 to 0.72) NPV 0.92 (0.82 to 0.97)
Berry 2018[20]	Secondary	Children	None	19.5	Blood agar	215	32	10	11	162	Sensitivity 0.76 (0.60 to 0.87) Specificity 0.94 (0.89 to 0.97) PPV 0.74 (0.56 to 0.86) NPV 0.94 (0.89 to 0.97)

continued

TABLE 14 Summary of test performance data by care setting (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
NADAL Strep A Strip – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
NADAL Strep A Cassette – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
NADAL Strep A Plus Cassette – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
NADAL Strep A Plus Strip – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
NADAL Strep A Scan – nal von minden GmbH											
nal von minden GmbH (MFR)[a]	Secondary	Children and adults	None	34.4	Blood agar	244	82	2	4	156	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.98 (0.93 to 0.99) PPV 0.95 (0.88 to 0.99) NPV 0.99 (0.95 to 1.00)
OSOM Strep A Strip – Sekisui Diagnostics											
Bura 2017[36]	Primary	Adults	Centor score of ≥ 2 points	22.7	Blood agar	101	22	1	2	76	Sensitivity 0.96 (0.76 to 1.00) Specificity 0.97 (0.90 to 1.00) PPV 0.92 (0.72 to 0.99) NPV 0.99 (0.92 to 1.00)
Llor 2009[44]	Primary	Adults	Centor score of ≥ 2 points	24.8	Blood agar	222	52	3	14	153	Sensitivity 0.95 (0.85 to 0.99) Specificity 0.92 (0.86 to 0.95) PPV 0.79 (0.69 to 0.86) NPV 0.98 (0.94 to 0.99)
Llor 2011[45]	Primary	Adults	Centor score of ≥ 2 points[b]	17.8	Blood agar	276	44	5	14	213	Sensitivity 0.90 (0.78 to 0.97) Specificity 0.94 (0.90 to 0.97) PPV 0.76 (0.65 to 0.84) NPV 0.98 (0.95 to 0.99)

continued

TABLE 14 Summary of test performance data by care setting (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Rogo 2011[49]	Secondary	Children	None	28.9	Blood agar	228	65	1	1	161	Sensitivity 0.98 (0.91 to 1.00) Specificity 0.99 (0.96 to 1.00) PPV 0.98 (0.91 to 1.00) NPV 0.99 (0.96 to 1.00)
Weinzierl 2018[54]	Secondary	Children	None	38.1	Blood agar	160	54	7	9	90	Sensitivity 0.89 (0.77 to 0.95) Specificity 0.91 (0.83 to 0.96) PPV 0.86 (0.74 to 0.93) NPV 0.93 (0.85 to 0.97)
QuikRead Go Strep A Kit – Orion Diagnostica											
Azrad 2019[34]	Secondary	NR	None	25.0	Streptococcal selective agar	100	20	5	20	55	Sensitivity 0.80 (0.59 to 0.92) Specificity 0.73 (0.62 to 0.83) PPV 0.50 (0.34 to 0.66) NPV 0.92 (0.81 to 0.97)
Stefaniuk 2017[52]	Primary	Children and adults[b]	None	45.3	Blood agar	95	39	4	8	44	Sensitivity 0.91 (0.78 to 0.97) Specificity 0.85 (0.72 to 0.93) PPV 0.83 (0.72 to 0.90) NPV 0.92 (0.81 to 0.97)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Alere TestPack Plus Cassette – Abbott Laboratories											
Dimatteo 2001[38]	Secondary	Adults	Centor score of ≥ 1 point	NR	Streptococcal selective agar	NR	NR	22	NR	361	NPV 0.94 (0.91 to 0.96)
Humair 2006[39]	Primary	Adults	Centor score of ≥ 2 points[b]	37.6	Blood agar	372	128	12	11	221	Sensitivity 0.91 (0.86 to 0.95) Specificity 0.95 (0.92 to 0.98) PPV 0.92 (0.87 to 0.95) NPV 0.95 (0.91 to 0.97)
Johansson 2003[40]	Primary	Children and adults	None	31.4	NR	144	46	7	4	87	Sensitivity 0.87 (0.74 to 0.94) Specificity 0.96 (0.89 to 0.99) PPV 0.92 (0.80 to 0.97) NPV 0.93 (0.85 to 0.97)
Johnson 2001[41]	Primary	Adults	None	NR	Blood agar	NR	445	NR	77	NR	PPV 0.85 (0.82 to 0.88)
Kurtz 2000[42]	Secondary	Children	None	31.1	Blood agar	257	64	16	13	164	Sensitivity 0.80 (0.71 to 0.89) Specificity 0.93 (0.89 to 0.97) PPV 0.83 (0.75 to 0.92) NPV 0.91 (0.87 to 0.95)
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	271	87	21	623	Sensitivity 0.76 (0.71 to 0.80) Specificity 0.97 (0.95 to 0.98) PPV 0.93 (0.89 to 0.95) NPV 0.88 (0.85 to 0.90)

continued

TABLE 14 Summary of test performance data by care setting (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Lindbæk 2004[43]	Primary	Children and adults	None	35.9	Streptococcal selective agar	306	106	4	27	169	Sensitivity 0.96 (0.91 to 0.99) Specificity 0.86 (0.80 to 0.91) PPV 0.80 (0.72 to 0.86) NPV 0.98 (0.94 to 0.99)
McIsaac 2004[46]	Primary	Children and adults[b]	McIsaac score of ≥ 2 points	29.0	Blood agar	787	189	39	5	554	Sensitivity 0.83 (0.77 to 0.88) Specificity 0.99 (0.98 to 1.00) PPV 0.97 (0.94 to 0.99) NPV 0.93 (0.91 to 0.95)
Penney 2016[48]	Secondary	Children	None	40.1	Streptococcal selective agar	147	45	14	0	88	Sensitivity 0.76 (0.65 to 0.87) Specificity 1.00 (0.95 to 1.00) PPV 1.00 (0.90 to 1.00) NPV 0.86 (0.78 to 0.92)
Rosenberg 2002[50]	Secondary	Children and adults	None	25.4	Blood agar	126	24	8	1	93	Sensitivity 0.75 (0.56 to 0.88) Specificity 0.99 (0.93 to 1.00) PPV 0.96 (0.78 to 1.00) NPV 0.92 (0.85 to 0.96)
Santos 2003[51]	Secondary	Children	None	30.6	Blood agar	49	11	4	2	32	Sensitivity 0.73 (0.45 to 0.91) Specificity 0.94 (0.79 to 0.99) PPV 0.85 (0.54 to 0.97) NPV 0.89 (0.73 to 0.96)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Valverde 2018[58]	Secondary	Children and adults	None	40.0	Blood agar	580	181	16	27	356	Sensitivity 0.92 (0.87 to 0.95) Specificity 0.93 (0.90 to 0.95) PPV 0.87 (0.82 to 0.91) NPV 0.96 (0.93 to 0.97)
bioNexia Strep A Dipstick – bioMérieux											
Pauchard 2013[57]	Secondary	Children	None	36.8	NR	193	60	11	11	111	Sensitivity 0.85 (0.74 to 0.92) Specificity 0.91 (0.84 to 0.95) PPV 0.85 (0.76 to 0.93) NPV 0.91 (0.86 to 0.96)
Sofia Strep A FIA – Quidel											
Lacroix 2018[23]	Secondary	Children	McIsaac score of ≥ 2 points	35.7	Blood agar	1002	305	53	31	613	Sensitivity 0.85 (0.81 to 0.89) Specificity 0.95 (0.93 to 0.97) PPV 0.91 (0.87 to 0.94) NPV 0.92 (0.90 to 0.94)
Alere i Strep A – Abbott Laboratories											
Berry 2018[20]	Secondary	Children	None	19.5	Blood agar	215	42	0	15	158	Sensitivity 1.00 (0.90 to 1.00) Specificity 0.91 (0.86 to 0.95) PPV 0.74 (0.60 to 0.84) NPV 1.00 (0.97 to 1.00)

continued

TABLE 14 Summary of test performance data by care setting (*continued*)

Study (first author and year of publication)	Care setting	Age group	Clinical tool score restriction	Strep A infections prevalence (%)	Reference type	*N*	TP (*n*)	FN (*n*)	FP (*n*)	TN (*n*)	Accuracy data (95% CI)
Cohen 2015[37]	Secondary	Children and adults[b]	None	30.3	Blood agar	481	141	6	18	316	Sensitivity 0.96 (0.91 to 0.98) Specificity 0.95 (0.91 to 0.97) PPV 0.89 (0.82 to 0.93) NPV 0.98 (0.96 to 0.99)
Weinzierl 2018[54]	Secondary	Children	None	38.1	Blood agar	160	60	1	0	99	Sensitivity 0.98 (0.90 to 1.00) Specificity 1.00 (0.95 to 1.00) PPV 1.00 (0.93 to 1.00) NPV 0.99 (0.94 to 1.00)
cobas Liat Strep A Assay – Roche Diagnostics											
Wang 2017[24]	Primary	Children	Centor score of ≥ 1 point	30.2	NR	427	126	3	20	278	Sensitivity 0.98 (0.93 to 0.99) Specificity 0.93 (0.90 to 0.96) PPV 0.86 (0.79 to 0.91) NPV 0.99 (0.97 to 1.00)

FN, false negative; FP, false positive; NR, not reported; TN, true negative; TP, true positive.
a The submission was provided by the company, and data were not included in the primary meta-analysis.
b Data were presented for subgroups of interest.

Alere TestPack Plus Cassette (Abbott Laboratories)

There were seven published studies that compared the performance of the Alere TestPack Plus Cassette with culture in a secondary care setting. One study did not report sufficient data to complete a 2 × 2 table.[38] Rosenberg *et al.*[50] and Valverde *et al.*[58] both examined a combination of children and adults, estimating sensitivities of 0.75 (95% CI 0.56 to 0.88) and 0.92 (95% CI 0.87 to 0.95), and specificities of 0.99 (95% CI 0.93 to 1.00) and 0.93 (95% CI 0.90 to 0.95), respectively. The four remaining studies included only children.[23,42,48,51] The sensitivities ranged from 0.73 (95% CI 0.45 to 0.91)[51] to 0.80 (95% CI 0.71 to 0.90)[42] and the specificities ranged from 0.93 (95% CI 0.89 to 0.97)[42] to 1.00 (95% CI 0.95 to 1.00).[48]

Five studies reported the accuracy of the Alere TestPack Plus Cassette in a primary care setting. One did not present complete 2 × 2 data.[41] One reported for adult populations: Humair *et al.*[39] estimated a sensitivity of 0.91 (95% CI 0.86 to 0.95) and a specificity of 0.95 (95% CI 0.92 to 0.98). Lindbæk *et al.*,[43] Johansson *et al.*[40] and McIsaac *et al.*[46] combined adults and children, and reported respective sensitivities of 0.94 (95% CI 0.90 to 0.99), 0.87 (95% CI 0.74 to 0.94) and 0.83 (95% CI 0.77 to 0.87) alongside specificities of 0.86 (95% CI 0.80 to 0.91), 0.96 (95% CI 0.89 to 0.99) and 0.99 (95% CI 0.98 to 1.00).

bioNexia Strep A Dipstick (bioMérieux)

Only data from a hospital setting were available for bioMérieux's bioNexia Strep A Dipstick. Pauchard *et al.*[57] estimated a sensitivity of 0.85 (95% CI 0.74 to 0.92) and a specificity of 0.91 (95% CI 0.84 to 0.95).

Sofia Strep A fluorescent immunoassay (Quidel)

One study compared Sofia Strep A FIA with culture in a hospital setting, with no GP data available. Lacroix *et al.*[23] reported a sensitivity of 0.85 (95% CI 0.81 to 0.89) and a specificity of 0.95 (95% CI 0.93 to 0.97).

Alere i Strep A (Abbott Laboratories)

Three studies compared the Alere i Strep A test with culture in a hospital setting. Berry *et al.*[20] and Weinzierl *et al.*[54] looked only at children, and estimated respective sensitivities of 1.00 (95% CI 0.90 to 1.00) and 0.98 (95% CI 0.90 to 1.00), and specificities of 0.91 (95% CI 0.86 to 0.95) and 1.00 (95% CI 0.95 to 1.00). Cohen *et al.*[37] examined both children and adults, and produced respective estimates of sensitivity and specificity of 0.96 (95% CI 0.91 to 0.98) and 0.95 (95% CI 0.91 to 0.97).

cobas Liat Strep A Assay (Roche Diagnostics)

Only data from a GP setting were available for the cobas Liat Strep A Assay. Wang *et al.*[24] reported that the test had a sensitivity of 0.98 (95% CI 0.93 to 0.99) and a specificity of 0.93 (95% CI 0.90 to 0.96).

Meta-analyses were conducted to indirectly compare the accuracy estimates of the child and adult populations for both the OSOM Strep A Strip and the Alere TestPack Plus tests, as these were the only tests with sufficient data.

Fitted to data for the TestPack Plus test, univariate models estimated a sensitivity of 0.90 (95% CI 0.83 to 0.96) and a specificity of 0.95 (95% CI 0.88 to 0.99) in a primary setting, compared with a sensitivity of 0.80 (95% CI 0.71 to 0.88) and a specificity of 0.97 (95% CI 0.94 to 0.99) in a secondary care setting.

The OSOM test also had sufficient studies to conduct univariate meta-analyses. However, the dichotomisation of studies into primary and secondary care settings was identical to the age dichotomisation. Univariate models fitted to the child/secondary care data estimated a sensitivity of 0.95 (95% CI 0.90 to 0.98) and a specificity of 0.97 (95% CI 0.95 to 0.99). Models fitted to the adult/primary care data estimated a sensitivity of 0.93 (95% CI 0.88 to 0.97) and a specificity of 0.94 (95% CI 0.91 to 0.97).

Conclusion

Test performance may vary depending on the care setting in which the test is being used. Further evidence is required.

Estimates of test accuracy for cost-effectiveness modelling

Having established that a number of factors may influence test accuracy, we sought to provide estimates for each test to be used in the cost-effectiveness modelling. This is consistent with the findings of Leeflang *et al.*[72] Ideally, estimates would have come from a meta-analysis of several studies specific to the scope population, by age group and setting. However, the evidence base was not sufficient to do this. In total, there were 21 tests × 3 age groups × 3 settings = 189 pairs of sensitivity and specificity estimates required. However, no data were available that were specific to the elderly or the pharmacy setting, or for three of the tests, meaning that there were just 18 × 2 × 2 = 72 potential pairs of estimates. Each estimate came from a combination of five studies or fewer. Factoring in the observed variation in test accuracy between studies alongside the scant evidence base, there is a significant likelihood that the final estimates may not be representative of the tests' true accuracy. There is a significant risk that a test with a larger evidence base published in peer-reviewed journal articles may be disadvantaged in comparison with a test in which there is only unpublished manufacturer information at high risk of bias.

We prioritised information from published studies [i.e. not those in manufacturer (submitted directly to NICE in response to a request for information) and FDA documents] in which data were available for patients restricted by throat score as per the scope. This provided accuracy data for one pair of estimates and relaxing the age group restriction provided another pair of estimates. It was necessary to relax the throat score restriction to obtain further estimates. An additional 13 pairs of estimates were obtained from studies that matched the age and care setting of the test. One further pair of estimates was obtained by using estimates from a mixed age population for an adult population. Relaxing the care setting and age restrictions allowed estimation of 24 pairs of test accuracy estimates for child and adult populations. Where there were multiple options for considering relaxing either age group or setting differences between studies and target population, factors such as sample size and number of studies were also considered. Studies in manufacturer responses to NICE and in FDA documents were included only if no other evidence was available for a specific test. Where these data are used, we consider the analysis to be at extremely high risk of bias and we do not recommend that these are sufficient to underpin any clinical decisions. The data from neither of these two sources matched a subgroup of interest or were restricted by throat score, but relaxing the ages and care settings provided estimates for a further 32 pairs.

A summary of the studies providing evidence for each estimate can be found in *Table 15*.

TABLE 15 Summary of studies providing estimates of test performance for economic modelling (colour coded for reliability)

	Primary care		Secondary care	
Test	**Children**	**Adult**	**Children**	**Adult**
Clearview Exact Strep A cassette	One abstract (Andersen *et al.*,[56] *n* = 353) – wrong setting, right age, wrong score restriction	One abstract (Andersen *et al.*,[56] *n* = 353) – wrong setting, wrong age, wrong score restriction	One abstract (Andersen *et al.*,[56] *n* = 353) – right setting, right age, wrong score restriction	One abstract (Andersen *et al.*,[56] *n* = 353) – right setting, wrong age, wrong score restriction
Clearview Exact Strep A dipstick – test strip	One abstract (Andersen *et al.*,[56] *n* = 353) – wrong setting, right age, wrong score restriction	One abstract (Andersen *et al.*,[56] *n* = 353) – wrong setting, wrong age, wrong score restriction	One abstract (Andersen *et al.*[56]) – right setting, right age, wrong score restriction	One abstract (Andersen *et al.*,[56] *n* = 353) – right setting, wrong age, wrong score restriction
BD Veritor Plus system group A Strep Assay – cassette	One study (Berry *et al.*,[20] *n* = 215) – wrong setting, right age, wrong score restriction	Two studies (Berry *et al.*,[20] *n* = 215; Azrad *et al.*,[34] *n* = 100) – wrong setting, wrong age, wrong score restriction	One study (Berry *et al.*,[20] *n* = 215) – right setting, right age, wrong score restriction	Two studies (Berry *et al.*,[20] *n* = 215; Azrad *et al.*,[34] *n* = 100) – wrong setting, wrong age, wrong score restriction

TABLE 15 Summary of studies providing estimates of test performance for economic modelling (colour coded for reliability) (*continued*)

Test	Primary care		Secondary care	
	Children	Adult	Children	Adult
Strep A Rapid Test – cassette	One MFR response (Biopanda Reagents, $n = 526$) – right setting, right age, wrong score restriction	One MFR response (Biopanda Reagents, $n = 526$) – right setting, wrong age, wrong score restriction	One MFR response (Biopanda Reagents, $n = 526$) – wrong setting, right age, wrong score restriction	One MFR response (Biopanda Reagents, $n = 526$) – wrong setting, wrong age, wrong score restriction
Strep A Rapid Test – test strip	No data	No data	No data	No data
NADAL Strep A – test strip	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – right setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – right setting, wrong age, wrong score restriction
NADAL Strep A – cassette	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction
NADAL Strep A plus – cassette	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction
NADAL Strep A plus – test strip	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction
NADAL Strep A scan test – cassette	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction	One MFR response (nal von minden GmbH, $n = 244$) – wrong setting, wrong age, wrong score restriction
OSOM Strep A test – test strip	One study (Llor *et al.*,[45] $n = 116$) – right setting, wrong age, right score restriction	One study (Llor *et al.*,[45] $n = 116$) – right setting, right age, right score restriction	Two studies (Rogo *et al.*,[49] $n = 228$; Weinzierl *et al.*,[54] $n = 160$) – right setting, right age, wrong score restriction	Five studies (Bura *et al.*,[36] $n = 101$; Llor *et al.*,[44] $n = 222$; Llor *et al.*,[45] $n = 276$, Rogo *et al.*,[49] $n = 228$; Weinzierl *et al.*,[54] $n = 160$) – wrong setting, wrong age, wrong score restriction
QuikRead Go Strep A test kit	One study (Stefaniuk *et al.*,[52] $n = 43$) – right setting, right age, wrong score restriction	One study (Stefaniuk *et al.*,[52] $n = 52$) – right setting, right age, wrong score restriction	Two studies (Azrad *et al.*,[34] $n = 100$; Stefaniuk *et al.*,[52] $n = 95$) – wrong setting, wrong age, wrong score restriction	Two studies (Azrad *et al.*,[34] $n = 100$; Stefaniuk *et al.*,[52] $n = 95$) – wrong setting, wrong age, wrong score restriction

continued

TABLE 15 Summary of studies providing estimates of test performance for economic modelling (colour coded for reliability) (*continued*)

Test	Primary care		Secondary care	
	Children	Adult	Children	Adult
Alere TestPack +Plus Strep A – cassette	One study (McIsaac *et al.*,[46] *n* = 494) – right setting, right age, wrong score restriction	One study (Humair *et al.*,[39] *n* = 224) – right setting, right age, right score restriction	Four studies (Kurtz *et al.*,[42] *n* = 257; Lacroix *et al.*,[23] *n* = 1002; Penney *et al.*,[48] *n* = 147; Santos *et al.*,[51] *n* = 49) – right setting, right age, wrong score restriction	One study and one abstract (Rosenberg *et al.*,[50] *n* = 126; Valverde *et al.*,[58] *n* = 580) – right setting, wrong age, wrong score restriction
bioNexia Strep A plus – cassette	No data	No data	No data	No data
bioNexia Strep A dipstick – test strip	One abstract (Pauchard *et al.*,[57] *n* = 193) – wrong setting, right age, wrong score restriction	One abstract (Pauchard *et al.*,[57] *n* = 193) – wrong setting, wrong age, wrong score restriction	One abstract (Pauchard *et al.*,[57] *n* = 193) – right setting, right age, wrong score restriction	One abstract (Pauchard *et al.*,[57] *n* = 193) – wrong setting, wrong age, wrong score restriction
bioNexia Strep A – cassette	No data	No data	No data	No data
Sofia Strep A FIA	One study (Lacroix *et al.*,[23] *n* = 1002) – wrong setting, right age, wrong score restriction	One study (Lacroix *et al.*,[23] *n* = 1002) – wrong setting, wrong age, wrong score restriction	One study (Lacroix *et al.*,[23] *n* = 1002) – right setting, right age, wrong score restriction	One study (Lacroix *et al.*,[23] *n* = 1002) – right setting, wrong age, wrong score restriction
Alere i Strep A	Three studies (Berry *et al.*,[20] *n* = 215; Cohen *et al.*,[37] *n* = 355; Weinzierl *et al.*,[54] *n* = 160) – wrong setting, right age, wrong score restriction	One study (Cohen *et al.*,[37] *n* = 126) – wrong setting, right age, wrong score restriction	Three studies (Berry *et al.*,[20] *n* = 215; Cohen *et al.*,[37] *n* = 355; Weinzierl *et al.*,[54] *n* = 160) – right setting, right age, wrong score restriction	One study (Cohen *et al.*,[37] *n* = 126) – right setting, right age, wrong score restriction
Alere i Strep A 2	One FDA study (Alere, *n* = 981) – wrong setting, wrong age, wrong score restriction	One FDA study (Alere, *n* = 981) – wrong setting, wrong age, wrong score restriction	One FDA study (Alere, *n* = 981) – wrong setting, wrong age, wrong score restriction	One FDA study (Alere, *n* = 981) – wrong setting, wrong age, wrong score restriction
cobas Liat Strep A Assay	One study (Wang *et al.*,[24] *n* = 427) – right setting, right age, wrong score restriction	One study (Wang *et al.*,[24] *n* = 427) – right setting, wrong age, wrong score restriction	One study (Wang *et al.*,[24] *n* = 427) – wrong setting, right age, wrong score restriction	One study (Wang *et al.*,[24] *n* = 427) – wrong setting, wrong age, wrong score restriction
Xpert Xpress Strep A	One FDA report and one MFR response (Cepheid, *n* = 618 and 577) – wrong setting, wrong age, wrong score restriction	One FDA report and one MFR response (Cepheid, *n* = 618 and 577) – wrong setting, wrong age, wrong score restriction	One FDA report and one MFR response (Cepheid, *n* = 618 and 577) – wrong setting, wrong age, wrong score restriction	One FDA report and one MFR response (Cepheid, *n* = 618 and 577) – wrong setting, wrong age, wrong score restriction

MFR, manufacturer; *n*, number of patients.

Notes

'MFR response' refers to unpublished accuracy data from the manufacturer provided within the NICE review process. Estimates are colour coded by number of studies, sample size of studies, source of information and population relevance.

Dark purple shading = very unreliable, aqua shading = moderately unreliable, orange shading = somewhat unreliable.

Accuracy of point-of-care tests using polymerase chain reaction to resolve discordant cases

Discordant results between point-of-care tests and culture were resolved using PCR in four studies.[20,24,37,73] All discrepant results between a point-of-care test and culture (point of care positive, culture negative and vice versa) were analysed in two of these studies.[20,24]

All of the 20 samples that were cobas Liat Strep A positive but culture negative were confirmed as positive by PCR and bidirectional sequencing. All three samples that were cobas Liat Strep A negative and reference culture positive were confirmed as positive by PCR and bidirectional sequencing.[24] Wang *et al.*[24] also examined the discrepancies between the TestPack Plus Strep A test and culture. All discordant results, that is the 20 cases positive by the test and negative by culture and the three cases that were test negative and culture positive, were positive according to PCR.

In evaluating the accuracy of the BD Veritor system, Berry *et al.*[20] also identified 21 discordant results with throat culture, including 11 positive on the index test but not culture, and 10 positive on culture but not the index test. PCR detected strep A in 6 of the 11 results that were positive by the BD Veritor System but negative by culture. PCR detected strep A in all of the 11 samples that were negative by the BD Veritor system but positive by culture. In the same population, Berry *et al.*[20] found that 14 of the 15 results that were positive for the Alere i Strep A test and negative for culture were found to be positive according to PCR. There were no reported occasions when the Alere i Strep A test gave a negative result when culture gave a positive result.

Similarly, Cohen *et al.*[37] and Lacroix *et al.*[23] analysed only some of the discrepancies between a point-of-care test and culture. Cohen *et al.*[37] identified a total of 24 discordant results between the Alere i Strep A test and culture. There were 18 positive samples on the Alere i Strep A test and not on culture, 13 of which were confirmed as positive by PCR, whereas the other five results were PCR negative. Four of the six cases that were positive on culture but not on Alere i Strep A were confirmed as negative by PCR.

Lacroix *et al.*[23] found 84 discordant results between Sofia Strep A FIA and culture (31 false positives and 53 false negatives). Eleven of the 31 false-positive samples were missing; hence, PCR assays could not be conducted for these samples. Eleven of those with samples present were confirmed as positive by PCR and nine were negative by PCR. Lacroix *et al.*[23] also found 21 results that were positive by TestPack Plus Strep A but negative by culture, nine of which were confirmed as positive by PCR. Eight were confirmed as PCR negative, leaving four missing samples, which precluded additional PCR assays. Lacroix *et al.*[23] did not provide test-specific results for the cases that were negative by rapid test and positive by culture.

Table 16 summarises the key findings from these analyses.

Interestingly, Lindbæk *et al.*[43] used a second culture medium (a liquid medium/broth) to resolve discrepant results between the TestPack Plus Strep A test (Abbott Laboratories) and microbiological culture (streptococcal selective agar). In this study, the second culture medium [colistin and oxolinic acid (COBA) + tryptic soy agar (TSA) sheep + sulfamethoxazole and trimethoprim (SXT) + Lim broth + first culture medium] detected strep A in 17 out of 27 (63%) patients who previously tested positive by the Alere TestPack +Plus Strep A test but negative by the first culture medium (Columbia agar + horse blood + COBA).

TABLE 16 Accuracy of point-of-care tests using PCR to arbitrate discordant results with culture

Study (first author and year of publication)	Index test	2 × 2 contingency tables		
		PCR +	PCR –	Total
Berry 2018[20]	Alere i Strep A test +, culture –	14	1	15
	Alere i Strep A test –, culture +	0	0	0
	Total	14	1	15
Berry 2018[20]	BD Veritor system +, culture –	6 (Berry *et al.*[20] also report 5)	5	11
	BD Veritor system –, culture +	10	0	10
	Total	16	5	21
Wang 2017[24]	cobas Liat Strep A Assay +, culture –	20	0	20
	cobas Liat Strep A Assay –, culture +	3	0	3
	Total	23	0	23
Cohen 2015[37]	Alere i Strep A +, culture –	13	5	18
	Alere i Strep A –, culture +	2	4	6
	Total	15	9	24
Lacroix 2018[23]	Sofia Strep A FIA +, culture –	11	9	31 (11 missing samples)
	Sofia Strep A FIA –, culture +	NR	NR	53
	Total	NR	NR	84
Lacroix 2018[23]	TestPack Plus Strep A +, culture –	9	8	21 (4 missing samples)
	TestPack Plus Strep A –, culture +	NR	NR	87
	Total	NR	NR	108

NR, not reported.

Direct comparison of point-of-care test accuracy with clinical scores

Six studies directly compared levels of test accuracy between point-of-care tests and clinical scores.[39,44–46,52,57] The results are summarised in *Table 17*. Sensitivity point estimates for clinical scores were higher for point-of-care tests than for rapid tests in two studies.[46,57] However, point estimates for sensitivity and particularly specificity of rapid tests (including TestPack Plus Strep A, OSOM Strep A and QuikRead Go Strep A tests) were generally higher. Sensitivity (0.829 to 0.946) and specificity (0.849 to 0.991) point estimates of point-of-care tests were consistently high when compared with point estimates for clinical scores (sensitivity 0.735 to 0.972; specificity 0.172 to 0.648).

Test failure rate

Five studies reported on test failure rate.[23,37,38,43,54] These five studies reported on three different point-of-care tests (Alere i, Testpack Strep A Plus and Sofia FIA Strep A). For the Alere i test, the test failure rate ranged from 0.0%[54] to 2.8%.[37] The TestPack Strep A Plus test failure rate ranged from 0.3%[38] to 1.3%.[43] The Sofia FIA strep test failure rate was reported as 4.7%.[23] Differences could be a result of environmental factors, such as staff training, as opposed to issues with the tests.

TABLE 17 Direct comparison of point-of-care test accuracy with clinical scores

Study (first author and year of publication)	Clinical score	Test accuracy statistics for clinical scores					Test accuracy statistics for index tests					
		Culture +	Culture –	Total	Sensitivity (95% CI)	Specificity (95% CI)	Index test	Culture +	Culture –	Total	Sensitivity (95% CI)	Specificity (95% CI)
Humair 2006[39]	Centor score of > 2 points	105	119	224	0.750 (0.678 to 0.822)	0.487 (0.423 to 0.551)	TestPack Plus Strep A+	128	11	139	0.914 (0.852 to 0.953)	0.953 (0.914 to 0.947)
	Centor score of ≤ 2 points	35	113	148			TestPack Plus Strep A–	12	221	233		
	Total	140	232	372			Total	140	232	372		
Llor 2009[44]	Centor score of > 2 points	47	104	151	0.855 (0.761 to 0.948)	0.377 (0.304 to 0.451)	OSOM Strep A+	52	14	66	0.946 (0.839 to 0.986)	0.916 (0.861 to 0.952)
	Centor score of ≤ 2 points	8	63	71			OSOM Strep A–	3	153	156		
	Total	55	167	222			Total	55	167	222		
Llor 2011[45]	Centor score of > 2 points	36	80	116	0.735 (0.587 to 0.846)	0.648 (0.581 to 0.709)	OSOM Strep A+	44	14	58	0.898 (0.770 to 0.962)	0.938 (0.897 to 0.933)
	Centor score of ≤ 2 points	13	147	160			OSOM Strep A–	5	213	218		
	Total	49	227	276			Total	49	227	276		
McIsaac 2004[46]	McIsaac score of > 2 points	193	375	568	0.847 (0.792 to 0.889)	0.329 (0.291 to 0.370)	TestPack Plus Strep A+	189	5	194	0.829 (0.772 to 0.874)	0.991 (0.978 to 0.997)
	McIsaac score of ≤ 2 points	35	184	219			TestPack Plus Strep A–	39	554	593		
	Total	228	559	787			Total	228	559	787		

continued

TABLE 17 Direct comparison of point-of-care test accuracy with clinical scores (*continued*)

Study (first author and year of publication)	Clinical score	Test accuracy statistics for clinical scores					Test accuracy statistics for index tests					
		Culture +	Culture –	Total	Sensitivity (95% CI)	Specificity (95% CI)	Index test	Culture +	Culture –	Total	Sensitivity (95% CI)	Specificity (95% CI)
Pauchard 2013[57]	McIsaac score of > 2 points	69	101	170	0.972 (0.893 to 0.995)	0.172 (0.112 to 0.253)	Strep A Rapid Test +	60	11	71	0.845 (0.735 to 0.914)	0.910 (0.841 to 0.952)
	McIsaac score of ≤ 2 points	2	21	23			Strep A rapid Test –	11	111	122		
	Total	71	122	193			Total	71	122	193		
Stefaniuk 2017[52]	Centor score of > 2 points	37	39	76	0.861 (0.714 to 0.942)	0.250 (0.145 to 0.392)	QuikRead Go Strep A+	39	8	47	0.907 (0.770 to 0.970)	0.846 (0.719 to 0.931)
	Centor score of ≤ 2 points	6	13	19			QuikRead Go Strep A–	4	44	48		
	Total	43	52	95			Total	43	52	95		

Proposed pathway (combined strategy of clinical score and point-of-care tests)

Test accuracy of combined clinical score and point-of-care test with culture as reference standard

None of the included studies evaluated the accuracy of a combined strategy of a sore throat clinical score (at the recommended NICE cut-off points of Centor/McIsaac score of ≥ 3 points or FeverPAIN score of ≥ 4 points) with a point-of-care test. This would require the combination of the two methods into a single procedure, in which positive results are produced by individuals with both a high clinical score and a positive point-of-care test, and negative results are given either by patients with a low clinical score or by patients with a high score but a negative point-of-care test. As shown in *Table 18*, Rosenberg *et al.*[50] provide the only available evidence that attempts to match the proposed pathway, but not at the recommended Centor cut-off point.

Other outcomes

No information was found on the number of appointments required per episode, morbidity, mortality, onward transmission of infection, health-related quality of life, patient satisfaction with the test or health-care professional satisfaction with the test.

Twelve studies reported on antibiotic-prescribing behaviours. RCTs and before-and-after studies have been described in *Appendix 5* (see *Tables 37* and *38* and *Figure 15*). The remaining eight studies that included one-armed cohorts or hypothetical antibiotic management are briefly summarised in *Antibiotic-prescribing behaviours: other study designs*.

Antibiotic-prescribing behaviours: randomised controlled trial evidence

There were three RCTs that reported on antibiotic use. All three trials found higher antibiotic prescription rates or use in control arms with no point-of-care test than in those with a point-of-care test.

TABLE 18 Accuracy of combined Centor score of 2 or 3 points and rapid testing with culture as the reference standard

		Test accuracy statistics for clinical scores				
Study (first author and year of publication)	Combined strategy	Culture +	Culture –	Total	Sensitivity for patients with a Centor score of 2 or 3 points	Specificity for patients with a Centor score of 2 or 3 points
Rosenberg 2002[50]	Centor score of 2 or 3 points AND TestPack Plus Strep A+	12	0	12	For patients with a Centor score of 2 or 3 points: 0.80 (95% CI 0.52 to 0.96) Overall: 0.88 (95% CI 0.71 to 0.96)	For patients with a Centor score of 2 or 3 points: 1.00 (95% CI 0.92 to 1.00) Overall: 0.78 (95% CI 0.68 to 0.86)
	Centor score of 2 or 3 points AND TestPack Plus Strep A–	3	44	47		
	Centor score of < 2 points AND no rapid test	1	29	30		
	Centor score of 4 points or 5 points AND no rapid test	16	21	37		
	Total	32	94	126		

In the UK RCT in primary care by Little *et al.*,[6] patients (mean ages 29 and 31 years across arms, no age range provided) in a primary health-care setting were randomly assigned to a delayed antibiotics control arm, a clinical score arm or a RADT arm (IMI TestPack, later known as Alere i Strep A test). In the delayed antibiotics control arm, depending on the severity of their presentation, patients were given antibiotics, given no antibiotics or given a delayed prescription of antibiotics to collect after 3–5 days if symptoms did not improve or worsened. This control group was there to represent current UK practice at the time. In the clinical score arm, patients were assessed using the FeverPAIN clinical scoring tool. Patients with scores of 0 or 1 points were not offered antibiotics. Immediate antibiotics were offered for patients with scores of ≥ 4 points; for patients with scores of 2 or 3 points, delayed antibiotics were offered. In the RADT group, all patients also received the clinical scoring tool. Those with scores of 0 or 1 points were not offered antibiotics or RADT, those with a score of 2 points were offered delayed antibiotics and those with scores of ≥ 3 points were given a RADT. All those with negative RADT results were not offered antibiotics. There were 207 patients in the delayed prescribing arm, of whom 79% (164/207) received a delayed prescription, 10% (21/207) received no antibiotics and 10% (21/207) received immediate antibiotics. In the clinical score arm, 41% (87/211) received a delayed prescription, 41% (87/211) received no antibiotics and 16% (33/211) received immediate antibiotics. In the RADT arm, there were fewer delayed prescription decisions, with only 23% (48/213) of patients receiving a delayed prescription; 59% (126/213) of patients were offered no antibiotics and 18% (38/213) were given immediate antibiotics. Patients reported antibiotic use of 46% (75/164) in the delayed prescription arm, 37% (60/161) in the clinical score arm and 35% (58/164) in the clinical score plus RADT arm. The total numbers in each arm were considerably lower for antibiotic use, indicating significant loss to follow-up, so these numbers should be interpreted with caution. Likewise, symptom severity was worse in the control arm, so effect sizes may be overestimates. This was a UK-based trial based in a primary health-care setting. For this reason, it is likely to be generalisable to the UK population.

The second trial was by Llor *et al.*[45] They included patients aged > 14 years (mean age 31.7 years) visiting primary health-care centres across Spain. This was a cluster RCT with the centre as the unit of randomisation. This form of randomisation can be prone to imbalancing baseline characteristics of patients; however, the authors reported no significant differences in baseline characteristics (such as gender, mean age and by clinical symptoms) between the participants across the intervention and control arms. Patients were randomised to either a control arm, in which patients were assessed using only clinical criteria (Centor), or an intervention arm, in which patients were assessed with both a Centor score and a RADT (OSOM Strep A test). In total, 54% (291/543) of patients were prescribed antibiotics. Antibiotics were more likely to be prescribed in the clinical score only arm, with GPs prescribing antibiotics in 64% (168/262) of patients, compared with 44% (123/281) in the RADT arm. There was a correlation between Centor score and antibiotic prescription rates across both groups, with more antibiotics prescribed to those with higher scores [score of 4 points – 80% antibiotics (37/46) in intervention arm and 96% (43/35) in the control arm compared with 16% (4/70) in intervention arm and 33.% (20/61) in control arm]. In the subgroup of interest to the UK population (those with Centor scores of ≥ 3 points), 74% (90/122) were given antibiotics in the intervention arm, compared with 85% (100/119) in the control arm. Antibiotic appropriateness is also discussed in the trial. Ninety-eight per cent (59/60) of patients with a positive RADT result were given antibiotics and 31% (69/225) of those with a negative test result received antibiotics. The authors determined that treatment was inappropriate (based on culture results) in 43% of patients (226/526), with 210 unnecessary prescriptions and 16 untreated cases. A total of 153 of these cases occurred in the control arm and 73 were in the RADT arm; however, the category of inappropriate decision (overprescribing or underprescribing) is not reported by trial arm.

The third trial was a four-armed cluster randomised trial in Canada by Worrall *et al.*[55] The trial included 40 physicians who were asked to consecutively recruit adult patients (aged ≥ 19 years, no further details reported). There was a control arm using usual clinical practice, an intervention arm using sore throat decision rules (STDR) (modified Centor), an intervention arm using a rapid test (RADT) and an

intervention arm using both STDR and RADT. In the STDR group, for clinical scores of ≤ 1 point no antibiotics were recommended, for scores of 3 or 4 points antibiotics were recommended and for scores of 2 points the prescribing decision lay with clinicians. In the combined STDR and RADT group, RADT was used only for patients with scores of 2. It is implied, although not explicitly stated, that all those in the RADT arm received a RADT. The authors found that 47% (247/533) of patients received antibiotics. By arm, 58% (82/141) of patients received antibiotics in the usual practice arm, compared with 55% (94/170) with Centor score alone, 27% (32/120) with rapid antigen testing alone and 38% (39/102) with combined rapid antigen testing and Centor score. As this was a cluster randomised trial and each arm included only 8–10 doctors, differences could be a result of differences between doctors rather than between strategies. In addition, they may be owing to differences in patients across arms. The study reports on the characteristics of the physicians only; we have no baseline patient data. Finally, the Canadian medical system differs to the UK system, so the results may not be generalisable.

There was no RCT evidence on molecular technologies and antibiotic-prescribing rates.

Antibiotic-prescribing behaviours: before-and-after studies

There was one study that was a before-and-after study assessing antibiotic-prescribing rates. The study by Bird *et al.*[35] analysed children (aged 6 months to 16 years) presenting to a UK paediatric emergency department with a sore throat. The study compared baseline data from October and November 2014 with prescribing rates in the following 2 years (August to November 2015 and September to November 2016) following the implementation of using both a McIsaac score and a RADT. Baseline data were collected retrospectively from a departmental audit, when it is implied that the method of diagnosis was just clinician examination, with the aim to assess the impact of a clinical scoring system and rapid test on prescribing rates. A rapid test could be requested only if there was a McIsaac score of ≥ 3 points. Following implementation, antibiotic-prescribing rates fell steeply, from 79% (166/210) at baseline to 24% (51/214) in year 1 and 28% (51/181) for the second year. However, seasonality may be a confounding factor, with higher prescribing rates over the later autumn months (October and November) than in late summer (August and September). Likewise, there may be some regression to the mean, as the high initial prescribing rates may have prompted the study but may be subject to fluctuations.

There were no two-armed cohort studies analysing molecular technologies and antibiotic-prescribing rates.

Antibiotic-prescribing behaviours: other study designs

There were an additional eight studies that reported antibiotic-prescribing behaviours in single-arm cohorts.[20,36,39,40,46,50,52,53] No comparative data were possible within these study designs, only hypothetical comparisons, so all of the results in this section should be interpreted with caution and considered less informative than the RCT results. In these cohort studies, patients received the same intervention; however, authors also determined hypothetical management scenarios and compared how this would have affected antibiotic-prescribing rates. Of the eight studies, three provided hypothetical rules, which does not help inform us on real-world behaviour. These three studies[39,46,53] have been included and briefly summarised but were not quality appraised. Five studies[20,36,40,50,52] reported on either what happened in the real world or what clinicians reported they would do. These studies suggested that using a rapid test would decrease antibiotic use by as little as 9% up to 74%.

Two of the five single-arm cohorts reported on real-world behaviour. The first study, by Stefaniuk *et al.*,[52] examined children and adults in a primary care setting in Poland. Forty-six per cent (44/96) of the study group were children aged 3–14 years and 25% (24/96) were adults aged 31–35 years (overall mean age was not provided). Ninety-eight per cent (46/47) of patients with a positive QuikRead Go Strep A test result received antibiotics and 24% (12/49) of patients with both a negative rapid test and a negative culture were treated with antibiotics.

The second study reporting on real-world behaviour, by Berry *et al.*,[20] compared BD Veritor testing with Alere i testing and a chart review to determine hypothetical impact of results on antibiotic use.

The study took place in paediatric outpatient clinics (mean age not reported) in the USA. Prescribing decisions were made with knowledge of the BD Veritor test results, but not of the Alere i test or culture. The authors found that 34% (73/215) of patients were prescribed antibiotics; of these, 25 patients were prescribed antibiotics at a clinic visit and antibiotics were later deemed to be inappropriate treatment (on the basis of culture results). Of these, 20 out of 25 (80%) patients were negative on BD Veritor, Alere i and culture, and five were positive with the BD Veritor only. Of the 215 who did not receive antibiotics, 13 BD Veritor-negative cases were identified by the authors as potential missed cases on the basis of PCR and Alere i positive results, of which six received antibiotics within 6 days of the original appointment. These analyses provide descriptive behaviour data using the BD Veritor test, but cannot be used to compare Alere and BD Veritor for appropriateness of prescribing behaviour as decisions were made using the BD Veritor and not the Alere i. This study using Alere i was the only study to use a molecular technology, and no prescribing behaviours were based on it; hence, there is no evidence on molecular technologies and antibiotic-prescribing rates.

Three of the single-arm cohort studies reported on hypothetical scenarios based around clinicians' decisions.[36,40,50] Bura *et al.*[36] examined a cohort of adults (median age 26 years, range 18–44 years) in primary care in Poland with Centor scores of > 2 points (this was a case–control design for test accuracy outcomes, but cohort for prescribing behaviour). All patients and controls were given a rapid test and culture. GPs could then choose whether or not to give antibiotic therapy. It is stated that this choice was not influenced by the research team; however, we cannot be certain of this as they were aware of the rapid test result. Clinicians were aware of the Centor score at the time of antibiotic prescribing. They found that 58% (59/101) of patients received an antibiotic. All RADT-positive patients received treatment, including two who were culture negative. In addition, 46% (35/77) of test-negative patients received antibiotics. They determined that 40% (23/59) of cases received an unnecessary antibiotic prescription. Unnecessary has been defined here as being culture negative. The authors also gave hypothetical management scenarios based on different Centor scores and scenarios. Antibiotics would be prescribed to 29% (11/38) of patients with a Centor score of 2 points, 62% (23/37) of patients with a Centor score of 3 points and 96% (25/26) of patients with a score of 4 points. They surmised that 23% (23/101) would have been treated using positive culture results alone and 24% (24/101) would have been treated using a rapid test, meaning that one person was mistakenly given antibiotics. However, 54% of those given antibiotics were treated for non-strep A. From the control group, one person would have been treated with antibiotics; additionally, other forms of streptococci were identified in 13 people from this group.

The study by Rosenberg *et al.*[50] was a one-armed prospective observational cohort in which all patients were given a clinical score (Centor), rapid test and culture. The study included patients older than 3 years [47% (59/126) aged 3–14 years, 50% (63/126) aged 15–44 years and 3% (4/126) aged ≥ 45 years] presenting to an emergency department in Canada. The authors also report physicians' clinical impressions and their hypothetical management. Authors report on score alone, physician examination alone, rapid test alone or rapid test for clinical scores of > 3 points. They found that physicians prescribed antibiotics to 37% (46/126) of patients, after obtaining the results of the rapid test; of these, 18 had negative culture results. They hypothesised that 20% (25/126) would have received antibiotics in the rapid test group, compared with 29% (37/126) in the clinical score group.

The last study, by Johansson *et al.*,[40] was a prospective observational single-armed cohort in which all patients received both a rapid test and culture and these results were compared with hypothetical management suggestions made by physicians. It included adult patients (aged 25–44 years, mean age not reported) reporting to primary health-care centres in Sweden. Physicians also clinically assessed patients, and gave hypothetical management suggestions based on their level of certainty for strep A (absolutely positive, positive, possibly positive, possibly negative, negative and absolutely negative). No results are clearly provided; however, 26% (24/94) of patients with a negative rapid test received treatment, but it is unclear how many of these were culture positive.

There were three additional studies[39,46,53] that reported on hypothetical prescribing decisions based on assumptions about doctors' behaviour; however, no real-world decisions were reported and doctors were not asked about behaviour.

Summary of the clinical effectiveness findings and implications for the health economic model

Overall, the findings reveal wide variations in the sensitivity (0.679 to 1.00) and specificity (0.733 to 1.00) estimates of point-of-care tests. These estimates were 0.829 to 0.946 for sensitivity and 0.849 to 0.991 for specificity in high-risk populations, including patients with Centor/McIsaac scores of > 2 points, which represents the population of interest. These estimates do not account for any of the unpublished manufacturer submissions.

Clinical scoring tools (FeverPAIN and Centor) have been proposed as a method by which clinicians can identify which patients are most likely to benefit from antibiotic use for sore throat.[8] These tools were developed to predict strep A (Centor and FeverPAIN), strep C (FeverPAIN) and strep G (FeverPAIN). Most studies making direct comparisons between sore throat clinical scoring tools and point-of-care tests indicated that sensitivity estimates were higher for the point-of-care tests, and that specificity was generally comparable between the two approaches.

A methodological limitation of the clinical scoring tools concerns the varying way in which they have been implemented across the included studies. For instance, different studies apply different clinical score cut-off points when recruiting patients. None of these studies matched the proposed pathway of care and treatment for patients with acute streptococcal pharyngitis, which would entail evaluating the test accuracy of a combined strategy of sore throat clinical scores at the recommended NICE thresholds (Centor/McIsaac score of ≥ 3 points or FeverPAIN score of ≥ 4 points) and point-of-care tests. This limitation potentially holds important economic implications, as attempts to model this proposed pathway may not be informed by the availability of empirical data. In addition, the over-representation of the TestPack Plus Strep A test relative to other point-of-care tests, as well as the overlap of patients across different age groups, potentially raises applicability concerns in the economic model.

Investigation of discordant results between the index tests and the reference standard of culture was available for several studies using PCR or culture. This analysis indicated that using culture as the reference standard may have resulted in underestimating sensitivity (specificity estimates derived using PCR were too variable to draw conclusions about potential overestimation/underestimation by culture). However, PCR can detect indolent strep A so the extent of this is unclear.

Data for test accuracy were sparse for each combination of test, population and setting. There were very few head-to-head (direct) comparison studies between index tests. There was heterogeneity between studies, the cause of which is unclear owing to a lack of direct comparison data of different age groups, settings or tests within the same study.

Test accuracy point estimates in manufacturers' submissions may be systematically higher than in the peer-reviewed literature, and the study characteristics are often unclear. Therefore, there is a risk of making inappropriate comparisons between tests in the economic model where one test has a range of peer-reviewed publications and another has manufacturer data only.

With the exception of a single study using the Sofia Strep A FIA test (failure rate 4.7%),[23] failure rates for point-of-care tests were generally low (0% to 2.8%) and unlikely to hold any major implications for the economic model, especially as the data for this outcome have not been reported in most of the included studies.

No evidence was found on time to antimicrobial prescribing decision, number of appointments required per episode and onward transmission of infection.

The findings suggest that RADT may help to reduce antibiotic prescription rates in patients who receive these tests compared with patients assessed using only a clinical scoring tool. The three RCTs addressing this question all found that up to 30% fewer antibiotics were prescribed following the administration of a RADT. No studies were identified that assessed the use of molecular technologies and antibiotic prescription rates.

Chapter 4 Cost-effectiveness

Systematic review of existing cost-effectiveness studies

Introduction

This chapter explores and reviews all published cost-effectiveness studies, including any existing economic models of the use of different rapid antigen detection or molecular tests (as listed in the final scope and protocol for detection of strep A in detail). Studies providing resource use, costs, utilities and probabilities that were useful to inform economic modelling were also identified.

Methods

Search strategy

A comprehensive search of the literature for published economic evaluations (including any existing models), cost studies and quality-of-life (utility) studies was carried out. The systematic search included searching the following electronic databases during January 2019 (on 22, 29 and 30 January 2019), and an updated search was conducted on all databases during March 2019 (on 7 and 13 March 2019):

- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (via OvidSP)
- Excerpta Medica database (EMBASE) (via OvidSP)
- NHS Economic Evaluation Database (NHS EED) and HTA database (via CRD)
- Science Citation Index and Conference Proceedings Citation Index – Science (via the Web of Science)
- Cost-Effectiveness Analysis (CEA) registry
- EconPapers [Research Papers in Economics (RePEc)]
- School of Health and Related Research Health Utilities Database (ScHARRHUD).

The search terms included economic and quality-of-life terms combined with either 'sore throat' or 'strep A'. No date limits were applied and databases were searched from inception. The search strategy was developed by an experienced information specialist, based on the clinical effectiveness review and with input from a health economist. Details of the full search strategies are provided in *Appendix 6*. In addition to these searches, any relevant cost-effectiveness studies identified during the clinical effectiveness review were brought to the attention of the reviewers and assessed for eligibility alongside the results of this review.

Assessment of eligibility

Citations and abstracts from the electronic online databases were exported into a citation software package (EndNote X7) and duplicate records were identified and removed. Two reviewers independently reviewed titles and abstracts to identify potentially relevant papers for inclusion. Any discrepancies were resolved by discussion.

Inclusion criteria

Only studies meeting the following inclusion criteria were included in the review:

- study type – fully published economic evaluations (including any economic models)
- population – people aged $\geq$ 5 years presenting to health-care providers in a primary care (GP surgeries, community pharmacies and walk-in centres) or secondary care (urgent care/walk-in centres and emergency departments) setting with symptoms of an acute sore throat

- intervention – 17 RADTs or four molecular tests (as described in *Chapter 1*, *Comparative technical overview of the point-of-care tests for group A* Streptococcus)
- comparator – antibiotic-prescribing decisions using clinical judgement and a clinical scoring tool such as FeverPAIN or Centor
- outcomes – cost–benefit or cost–consequences or cost-effectiveness or cost–utility studies reporting outcomes as cost–consequence measures or clinical effectiveness measures or utility measures [utility, EuroQol-5 Dimensions (EQ-5D) or Short Form questionnaire-6 Dimensions score or quality-adjusted life-years (QALYs)].

Exclusion criteria

Studies meeting the following exclusion criteria were excluded from the review:

- non-English-language publications
- studies not in humans
- studies not in strep A or sore throat
- studies with the wrong test or no specified test
- studies that were not full economic evaluations (incremental costs and incremental benefits).

Studies that provided useful information for the economic model, such as resource use, costs, utilities and probabilities, were retained but were not included in this review.

Data extraction

Data extraction was carried out by one reviewer using standardised data extraction sheets and was then checked by a second reviewer. Data extracted included the following information:

- study details – study title, author names, source of publication, language and publication type
- baseline characteristics – population (and subgroups), intervention, comparators, outcomes, study design, setting and location and type of economic evaluation
- methods – study perspective, time horizon, discount rate, measurement of effectiveness, measurement and valuation of preference-based outcomes, resource use and costs, currency, price date and conversion, model type, assumptions and analytical methods
- results – study parameters, incremental costs and outcomes and reporting of uncertainty
- discussion – study findings, limitations, generalisability and conclusions
- other – sources of funding, conflicts of interest and any comments.

Data synthesis

Information extracted from the included studies was summarised and tabulated. Findings from individual studies were compared narratively.

Quality assessment

The quality of full economic evaluation studies that were identified was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist by one reviewer and cross-checked by a second reviewer. The CHEERS checklist comprises six dimensions (title and abstract, introduction, methods, results, discussion and other); under these dimensions, a series of questions check whether or not the criteria have been clearly reported.[74] If the studies included any model-based economic evaluations, they were further critically appraised using the framework on quality assessment for economic modelling developed by Phillips *et al.*[75] The framework assesses models under the dimensions of structure, data and consistency and whether or not the criteria have been clearly reported.

Results

Search results

The literature search identified 6980 records through electronic database searches and other sources. After removing duplicates, 2756 records were screened for inclusion. One article was found via our clinical effectiveness search. Based on title and abstract sift only, 2737 records were excluded. The remaining 19 records were included for full-text screening. A further 16 articles were excluded at the full-text stage, as these studies did not contain a full economic evaluation or specify the right test (see *Appendix 7* for further comments).

The literature search identified three studies that had evidence pertaining to incremental costs and outcomes: Bura *et al.*,[36] Humair *et al.*[39] and Little *et al.*[76] (*Figure 11*).

The economic information from the first two studies has been summarised below, as there was not enough information for a full data extraction (see *Appendix 8*). These two studies did not explicitly state the following: study perspective, time horizon, type of economic evaluation, measurement of effectiveness or analytical methods. Bura *et al.*[36] was a prospective case–control study consisting of 101 adults (aged 18–44 years) who went to GP clinics in Poland because of sore throat lasting no longer than 7 days. Control participants ($n = 101$) were volunteers from the same area, who were matched to cases according to their age and sex. The study was conducted over 1 year. The OSOM Strep A test (Sekisui Diagnostics) in conjunction with throat culture was compared with Centor and throat culture to confirm presence of strep A. The costs of diagnosing and treating strep A included symptomatic treatment, test cost (€1.39), a single culture to identify strep A, antibiotic therapy and antimicrobial medications. Economic analysis of five strategies were compared for treating patients with strep A in terms of cost per patient with appropriate strep A treatment ranged from €2.89 (for treat only RADT positive cases) to €6.93 [for treat only strep A + (culture-positive) cases].

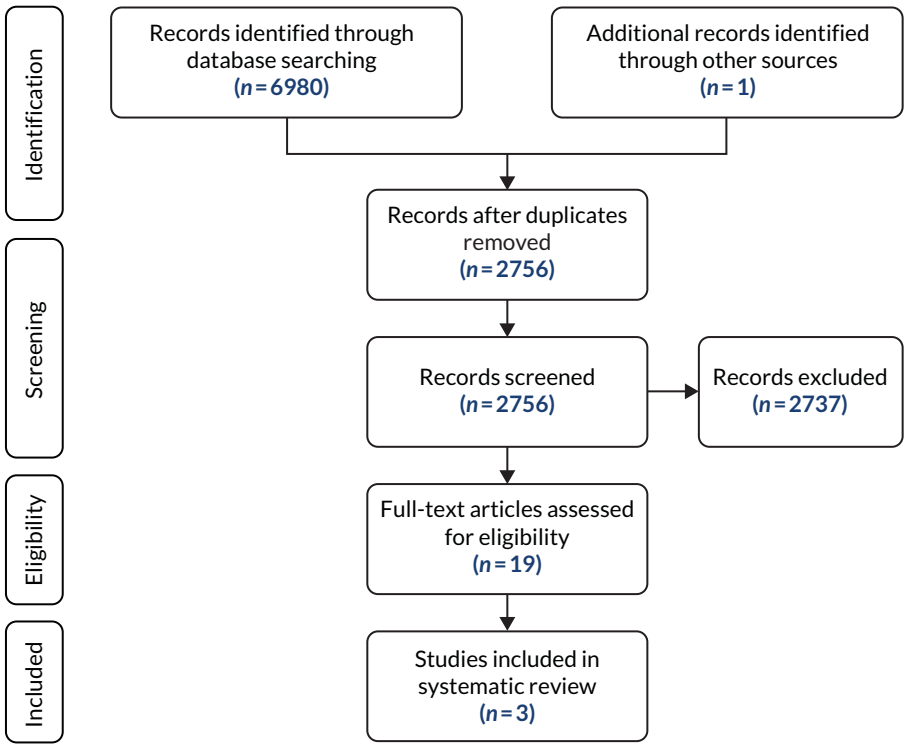

FIGURE 11 The PRISMA flow diagram for economic evaluation studies.

The authors concluded that the use of the rapid test significantly increases the number of people with strep A-related pharyngitis to be treated with antibiotics.

Humair *et al.*[39] was a prospective cohort study consisting of 372 adults (aged 15–65 years) who were treated at a GP clinic in Switzerland. The Alere TestPack +Plus Strep A (Abbott Laboratories) was compared with throat culture. A decision tree model was used to compare antibiotic prescription for five strategies. Information used in the decision model included antibiotic rate for appropriate use, overuse in patients without strep A, underuse in patients with strep A, appropriate treatment for patients with strep A and without treatment in patients without strep A. The model did not consider quality of life, complications or adverse drug effects. Costs were in US$ in 2002 prices. Costs included a 10-day course of penicillin, a test cost of $5.00 and $18.00 for throat culture. The authors found that systematic throat culture had the highest rates of appropriate treatment, whereas empirical treatment in patients with clinical scores of 3 or 4 resulted in the most antibiotic overuse. The cost per case appropriately treated ranged from $15.30 (systematic rapid test) to $32.40 (systematic throat culture). Sensitivity analyses were conducted to check the robustness of results. The authors concluded that the rapid test is a valid test for diagnosis of strep A.

Little *et al.*[76] conducted an economic analysis alongside a RCT in the UK, which included both adults and children with acute sore throat who were seen in primary care clinics (see *Appendix 8*). They compared randomised patients with targeted antibiotic use according to (1) delayed antibiotics (control group), (2) clinical score using FeverPAIN or (3) RADT – Alere TestPack +Plus Strep A (Abbott Laboratories) used according to clinical score. The analysis was from an NHS perspective and the time horizon was short (14 and 28 days); hence, long-term effects were not captured. Health-related quality of life was evaluated using the EQ-5D. QALYs were adjusted for baseline differences and were calculated using mean EQ-5D scores obtained from the 14-day diary records. It was assumed that the health-related quality of life changes linearly over time. The analysis included a cost-effectiveness analysis (cost per change in symptom severity) and a cost–utility analysis (cost per QALY). Cost-effectiveness acceptability curves (CEACs) were generated using bootstrapping with 5000 samples.

The mean symptom scores were adjusted for baseline differences. For the cost-effectiveness analysis, the clinical score group dominated both the delayed antibiotic group and the RADT group, as it was more clinically effective (lower symptom score) and less costly. However, the point estimate of symptom score and the corresponding 95% CIs for clinical score and RADT groups were quite close. The CEAC showed that if the value of a 1-point change in the symptom score was varied between £0 and £500, and it was found that over the entire range the clinical score group was most likely to be cost-effective. In the cost–utility analysis, the delayed group was dominated by the clinical score group for both time frames. The incremental cost-effectiveness ratio (ICER) for the RADT group compared with clinical score group was £74,286 for the 14-day time frame and £24,528 for the 28-day time frame.

Quality assessment

The quality of the reporting of the economic analysis of the three studies was assessed using the 25-point CHEERS checklist[74] and is provided in *Table 19*. The Little *et al.*[76] article was comprehensively reported: 22 of the 25 statements (88.0%) were a 'yes', one statement (4.0%) was not completed and two statements (8.0%) did not apply.

Summary

The cost-effectiveness search highlighted three studies that used the RADTs as identified in the NICE scope and were classed as economic evaluations. Of these three studies, only one allowed a full data extraction and was classed as a high-quality economic evaluation when checked against the CHEERS reporting tool. In *Chapter 5*, we build a de novo economic model comparing the different tests identified in the NICE scope for the various settings for patients with strep A.

TABLE 19 The CHEERS quality assessment checklist for economic evaluation studies

Assessment	Bura *et al.*[36]	Humair *et al.*[39]	Little *et al.*[76]
Title	N	N	Y
Abstract	Y	Y	Y
Introduction			
Background and objectives	Y	Y	Y
Methods			
Target population and subgroups	Y	Y	Y
Setting and location	Y	Y	Y
Study perspective	N	N	Y
Comparators	Y	Y	Y
Time horizon	N	N	Y
Discount rate	NA	N	NA
Choice of health outcomes	P	P	Y
Measurement of effectiveness	N	N	Y
Measurement and valuation of preference-based outcomes	N	N	Y
Estimating resources and costs	P	P	Y
Currency, price date and conversion	N	Y	Y
Choice of model	NA	N	NA
Assumptions	NA	N	Y
Analytical methods	P	N	Y
Results			
Study parameters	N	N	Y
Incremental costs and outcomes	Y	Y	Y
Characterising uncertainty	N	P	Y
Discussion			
Study findings	Y	Y	Y
Limitations	Y	Y	Y
Generalisability	N	N	Y
Other			
Source of funding	Y	N	Y
Conflicts of interest	Y	N	N

N, not reported; NA, not applicable; P, partially reported; Y, yes reported.

Cost-effectiveness methods and results

Modelled population

The population of interest is people aged ≥ 5 years presenting to health-care providers in a primary (GP surgeries and walk-in centres), secondary (urgent care/walk-in centres and emergency departments) or pharmacy care setting with symptoms of an acute sore throat identified as most likely to benefit from antibiotic treatment on the basis of clinical scoring algorithm (FeverPAIN score of 4 or 5 points, or a

Centor score of 3 or 4 points). Potential subgroups identified in the NICE scope included children (aged 5–14 years), adults (aged 15–75 years) and the elderly (aged > 75 years). However, the analyses have been restricted to adults and children owing to a lack of evidence on test accuracy among the elderly patient population.

Model structure

A decision tree model from the perspective of the UK NHS and Personal Social Services was developed to estimate the costs and QALYs associated with point-of-care testing in conjunction with clinical scoring tools, such as the Centor and FeverPAIN score for strep A, compared with clinical assessment incorporating clinical scoring tools alone (usual care).[77]

The model structure, as depicted in *Figures 12–14*, makes use of a decision tree to model potential care pathways associated with a suspected strep A infection/sore throat presentation under the intervention (point-of-care testing and clinical scoring tools) and usual-care (clinical scoring tools alone) conditions.

Previous economic evaluations of management strategies for streptococcal pharyngitis have estimated that up to 76.5 quality-adjusted life-days could be lost as a result of rare but serious complications of the infection, such as acute rheumatic fever.[78–80] Thus, for this economic model we have assumed a 1-year time horizon in which we model only one episode of strep A per patient and we have assumed that this time horizon is sufficient to capture the impact of rare but serious complications of the infection on economic costs and outcomes. This differs from the stated time horizon of 14 days originally conceived in the EAG protocol for this self-limiting illness for which the majority of cases would be expected to resolve satisfactorily.

The model takes account of the prevalence of disease in the modelled population, the test accuracy of clinical scoring algorithms and point-of-care tests, the proportion of patients treated with immediate and delayed antibiotics who are given a positive or negative clinical score and/or test result (prescribing behaviour of treating clinicians) and the probability of developing important but rare complications of the infection (i.e. suppurative complications, such as peritonsillar abscess and quinsy,[81] and non-suppurative complications, such as acute rheumatic fever).[82] Penicillin-induced rash and anaphylactic complications of penicillin are incorporated as adverse effects of treatment.[81,83]

The model estimated costs in 2017/18 prices. Economic costs accrued over the modelled time horizon are from resource use associated with simulated care pathways. They include the costs of the point-of-care tests (including additional cost of confirmatory throat culture for a negative test result), GP consultations, antimicrobial therapy and treatment for strep A-related complications and the unwanted effects of penicillin. QALYs are calculated as a weighted sum of the difference between the utility decrements associated with strep A infection and related complications and the general UK population utility norms, weighted by the modelled time horizon in years. No discounting was applied to costs and benefits owing to the 1-year time horizon.

The base-case analysis assumes that patients presenting with suspected strep A in the usual-care arm receive immediate or delayed antimicrobial treatment based on clinical assessment and outcome of clinical scoring algorithm indicating possible strep A infection. We assumed a score of ≥ 3 points on the Centor (or FeverPAIN score of ≥ 4 points) as the threshold for commencing immediate antibiotics (or testing for those in the intervention arm), as shown in *Figure 1* and in line with recent NICE guidance on antimicrobial prescribing for acute sore throat infections.[8]

We explored the impact of alternative thresholds (Centor score of ≥ 2 points and ≥ 1 point) for commencing antibiotic treatment and on testing. These alternative thresholds have differing performance (sensitivity and specificity) to the Centor score of ≥ 3 points; hence, they could be considered as assessing an alternative performance of the Centor tool. For the intervention arm, we assumed that patients presenting with

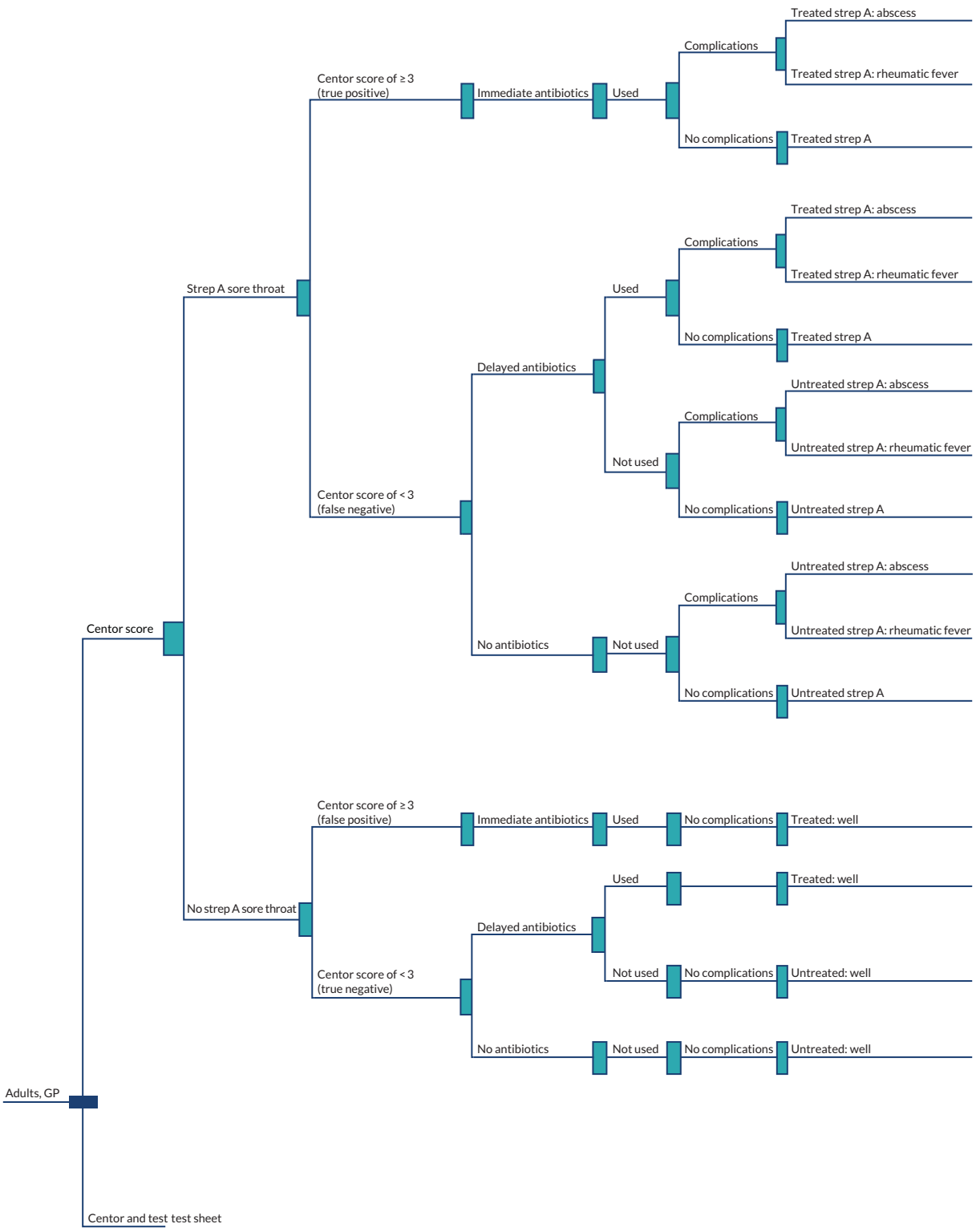

FIGURE 12 Strep A model part 1.

suspected strep A will be screened first using a clinical scoring tool for signs and symptoms of the infection. Those screening positive (i.e. Centor score of ≥ 3 points or FeverPAIN score of ≥ 4 points) are offered a point-of-care test followed by immediate antibiotics if testing indicates positive strep A infection. Those screening negative according to a clinical scoring algorithm or test are offered delayed antibiotic prescription with a probability of 0.49 and 0.29 in the usual-care and test arms, respectively, based on the PRImary care Streptococcal Management (PRISM) trial data.[6]

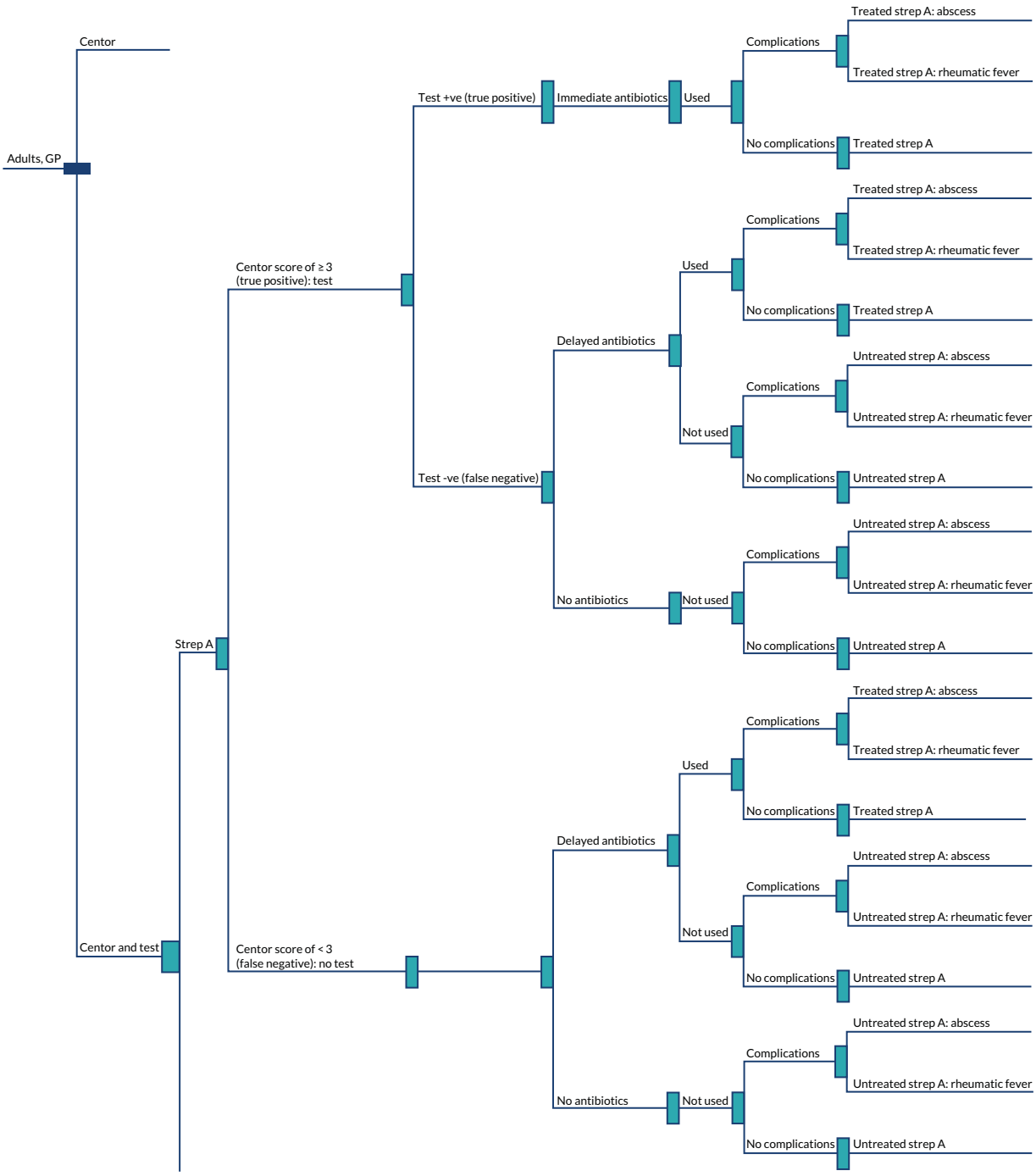

FIGURE 13 Strep A model part 2.

Over the 1-year time horizon, patients with suspected strep A infection receiving either immediate antibiotics or delayed antibiotics can make a complete recovery or go on to develop complications requiring a period of hospital stay. The risk of developing serious complications related to strep A is modelled as a function of antimicrobial treatment so that those patients who are correctly diagnosed and appropriately treated present a lower risk of serious strep A complications than do those who are incorrectly diagnosed who receive no antimicrobial treatment. Separate models (each with the same underlying structure depicted in *Figures 12–14*) are specified for adults and children in primary and secondary care settings.

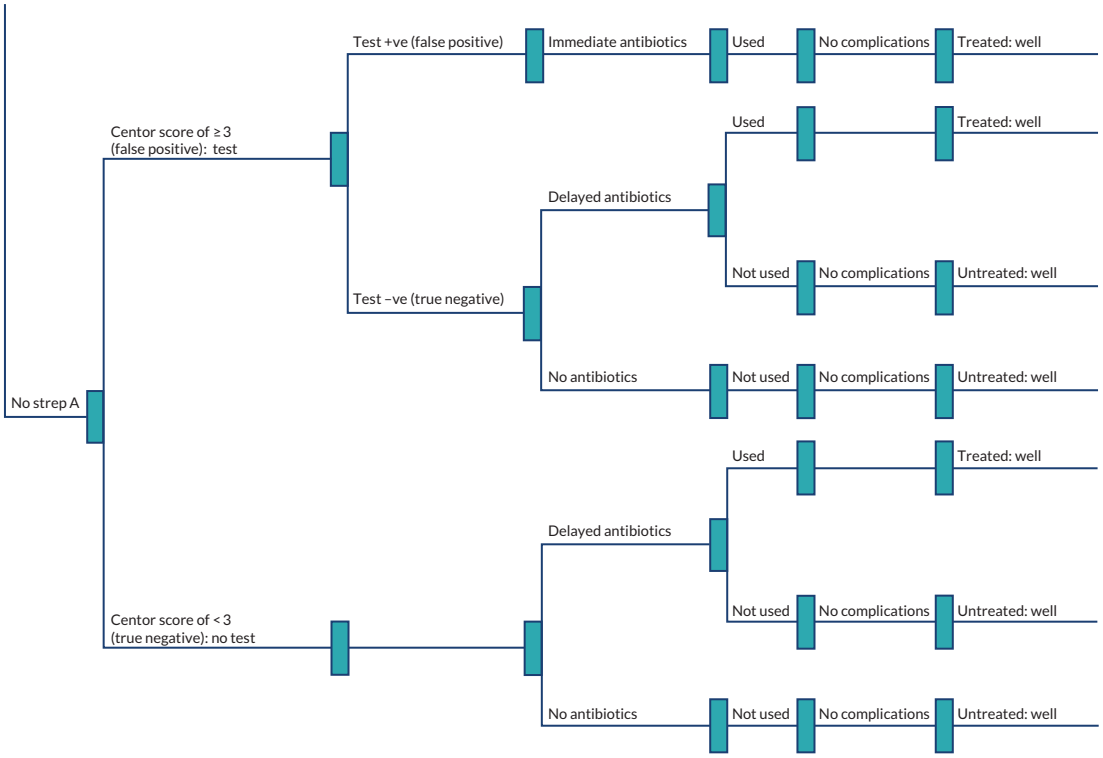

FIGURE 14 Strep A model part 3.

Details of the methodology used to derive parameter inputs and the data sources used to inform estimates are discussed in the following sections.

Effectiveness evidence used in the economic model

Accuracy of clinical scoring algorithms (all models)

Accuracy in the usual-care arm was based on estimates of sensitivity and specificity of the Centor score taken from a published meta-analysis of 12 studies by Aalbers *et al.*[84] *Table 20* summarises the reported estimates of sensitivity and specificity of the Centor score at cut-off points of ≥ 1, ≥ 2, ≥ 3 and 4 points for positive strep A infection. The base-case model used the estimates at a cut-off point of ≥ 3 points for a positive result and < 3 points for a negative result. At this threshold, the Centor score has a sensitivity of 0.49 (95% CI 0.38 to 0.60) and a specificity of 0.82 (95% CI 0.72 to 0.88). Alternative thresholds on the Centor score were explored in sensitivity analyses.[84] However, we were unable to evaluate the FeverPAIN clinical score owing to a lack of accuracy estimates in a format suitable for the economic model (i.e. sensitivity and specificity of the FeverPAIN at a cut-off point of ≥ 4 points).

TABLE 20 Diagnostic accuracy of the Centor score based on meta-analysis of 12 studies reported by Aalbers *et al.*[84]

Centor threshold (points) for positive strep A infection	Sensitivity (95% CI)	Specificity (95% CI)	Number of primary studies included in the meta-analysis	Distributional form in model
≥ 1	0.95 (0.91 to 0.97)	0.18 (0.12 to 0.26)	11	Normal (logit scale)
≥ 2	0.79 (0.71 to 0.86)	0.55 (0.45 to 0.65)	12	Normal (logit scale)
≥ 3	0.49 (0.38 to 0.60)	0.82 (0.72 to 0.88)	11	Normal (logit scale)
4	0.18 (0.12 to 0.27)	0.95 (0.92 to 0.97)	11	Normal (logit scale)

Accuracy of point-of-care tests

Estimates of test accuracy for the point-of-care tests obtained from our systematic review with and without meta-analyses are summarised in *Table 21* by test, clinical setting (primary care) and patient population (adults and children). When no studies reporting accuracy data were identified in

TABLE 21 Test accuracy of point-of-care tests used in the economic model in primary care

Test ID	Test name	Manufacturer	Sensitivity (95% CI)	Specificity (95% CI)	Distribution	Data source (first author and year of publication)
Adults						
1	Clearview Exact Strep A cassette	Abbott Laboratories	0.68 (0.54 to 0.8)	0.95 (0.92 to 0.97)	Normal (logit)	One abstract (Andersen 2003[56])
2	Clearview Exact Strep A dipstick – test strip	Abbott Laboratories	0.68 (0.54 to 0.8)	0.95 (0.92 to 0.97)	Normal (logit)	One abstract (Andersen 2003[56])
3	BD Veritor Plus system group A Strep Assay – cassette	Becton Dickinson	0.78 (0.67 to 0.87)	0.9 (0.86 to 0.93)	Normal (logit)	Two studies (Berry 2018[20] and Azrad 2019[34])
4	Strep A Rapid Test – cassette	Biopanda Reagents	0.95 (0.9 to 0.98)	0.98 (0.96 to 0.99)	Normal (logit)	One manufacturer response to NICE
5	Strep A Rapid Test – test strip	Biopanda Reagents				No data
6	NADAL Strep A – test strip	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
7	NADAL Strep A – cassette	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
8	NADAL Strep A plus – cassette	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
9	NADAL Strep A plus – test strip	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
10	NADAL Strep A scan test – cassette	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
11	OSOM Strep A test – test strip	Sekisui Diagnostics	0.92 (0.76 to 0.98)	0.96 (0.89 to 0.99)	Normal (logit)	One study (Llor 2011[45])
12	QuikRead Go Strep A test kit	Orion Diagnostica	1 (0.85 to 1)	0.79 (0.6 to 0.92)	Normal (logit)	One study (Stefaniuk 2017[52])
13	Alere TestPack +Plus Strep A – cassette	Abbott Laboratories	0.95 (0.89 to 0.98)	0.94 (0.88 to 0.98)	Normal (logit)	One study (Humair 2006[39])
14	bioNexia Strep A plus – cassette	bioMérieux				No data
15	bioNexia Strep A dipstick – test strip	bioMérieux	0.85 (0.74 to 0.92)	0.91 (0.84 to 0.95)	Normal (logit)	One abstract (Pauchard 2003[57])

TABLE 21 Test accuracy of point-of-care tests used in the economic model in primary care (*continued*)

Test ID	Test name	Manufacturer	Sensitivity (95% CI)	Specificity (95% CI)	Distribution	Data source (first author and year of publication)
16	Biosynex Strep A – cassette	Biosynex				No data
17	Sofia Strep A FIA	Quidel	0.85 (0.81 to 0.89)	0.95 (0.93 to 0.97)	Normal (logit)	One study (Lacroix 2018[23])
18	Alere i Strep A	Abbott Laboratories	0.95 (0.74 to 1)	0.97 (0.92 to 0.99)	Normal (logit)	One study (Cohen 2015[37])
19	Alere i Strep A 2	Abbott Laboratories	0.98 (0.96 to 1)	0.93 (0.91 to 0.95)	Normal (logit)	One FDA report
20	cobas Liat Strep A Assay	Roche Diagnostics	0.98 (0.93 to 1)	0.93 (0.9 to 0.96)	Normal (logit)	One study (Wang 2017[24])
21	Xpert Xpress Strep A	Cepheid	1 (0.99 to 1)	0.94 (0.92 to 0.96)	Normal (logit)	One manufacturer response to NICE and one FDA report
Children						
1	Clearview Exact Strep A cassette	Abbott Laboratories	0.68 (0.54 to 0.8)	0.95 (0.92 to 0.97)	Normal (logit)	One study (Andersen 2003[56])
2	Clearview Exact Strep A dipstick – test strip	Abbott Laboratories	0.68 (0.54 to 0.8)	0.95 (0.92 to 0.97)	Normal (logit)	One study (Andersen 2003[56])
3	BD Veritor Plus system group A Strep Assay – cassette	Becton Dickinson	0.76 (0.61 to 0.88)	0.94 (0.89 to 0.97)	Normal (logit)	One study (Berry 2018[20])
4	Strep A Rapid Test – cassette	Biopanda Reagents	0.95 (0.9 to 0.98)	0.98 (0.96 to 0.99)	Normal (logit)	One manufacturer response to NICE
5	Strep A Rapid Test – test strip	Biopanda Reagents				No data
6	NADAL Strep A – test strip	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
7	NADAL Strep A – cassette	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
8	NADAL Strep A plus – cassette	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
9	NADAL Strep A plus – test strip	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
10	NADAL Strep A scan test – cassette	nal von minden GmbH	0.98 (0.92 to 1)	0.98 (0.94 to 0.99)	Normal (logit)	One manufacturer response to NICE
11	OSOM Strep A test – test strip	Sekisui Diagnostics	0.94 (0.89 to 0.98)	0.95 (0.91 to 0.98)	Normal (logit)	One study (Llor 2011[45])
12	QuikRead Go Strep A test kit	Orion Diagnostica	0.80 (0.56 to 0.94)	0.91 (0.72 to 0.99)	Normal (logit)	One study (Stefaniuk 2017[52])

continued

TABLE 21 Test accuracy of point-of-care tests used in the economic model in primary care (*continued*)

Test ID	Test name	Manufacturer	Sensitivity (95% CI)	Specificity (95% CI)	Distribution	Data source (first author and year of publication)
13	Alere TestPack +Plus Strep A – cassette	Abbott Laboratories	0.86 (0.79 to 0.91)	0.99 (0.97 to 1)	Normal (logit)	One study (McIsaac 2004[46])
14	bioNexia Strep A plus – cassette	bioMérieux				No data
15	bioNexia Strep A dipstick – test strip	bioMérieux	0.85 (0.74 to 0.92)	0.91 (0.84 to 0.95)	Normal (logit)	One abstract (Pauchard 2013[57])
16	Biosynex Strep A – cassette	Biosynex				No data
17	Sofia Strep A FIA	Quidel	0.85 (0.81 to 0.89)	0.95 (0.93 to 0.97)	Normal (logit)	One study (Lacroix 2018[23])
18	Alere i Strep A	Abbott Laboratories	0.98 (0.95 to 1)	0.96 (0.89 to 1)	Normal (logit)	Three studies (Berry 2018,[20] Cohen 2015[37] and Weinzierl 2018[54])
19	Alere i Strep A 2	Abbott Laboratories	0.98 (0.96 to 1)	0.93 (0.91 to 0.95)	Normal (logit)	One FDA report
20	cobas Liat Strep A Assay	Roche Diagnostics	0.98 (0.93 to 1)	0.93 (0.9 to 0.96)	Normal (logit)	One study (Wang 2017[24])
21	Xpert Xpress Strep A	Cepheid	1 (0.99 to 1)	0.94 (0.92 to 0.96)	Normal (logit)	One manufacturer response to NICE and one FDA report

our systematic review, we obtained the estimates from either the manufacturer website or the manufacturer submissions (submitted directly to NICE in response to a request for information). Test accuracy data were available for six (28.6%) of the 21 tests from published sources identified in the clinical effectiveness review; a further four tests (19%) had accuracy data from both published sources and manufacturer submissions, six tests (27.6%) had only manufacturer data and two tests (9.5%) had FDA data. Test accuracy data were not available for the three (14.3%) remaining tests (Biopanda Reagents' Strep A Rapid Test strip, bioNexia Strep A cassette and bioNexia Strep A plus cassette). Two of the three tests (bioNexia Strep A cassette and bioNexia Strep A plus cassette) were excluded from the economic modelling of individual tests owing to a lack of test accuracy data. The accuracy of Biopanda Reagents' Strep A Rapid Test strip was assumed to be equal to that of the cassette version of this test, for which accuracy estimates were available. In general, estimates of sensitivity and specificity obtained from the published sources tended to be variable and lower than those provided by the manufacturer. For example, sensitivity of point-of-care testing in adults based on the published sources ranged from 0.68, for Abbott Laboratories' Clearview Exact Strep A cassette, to 1.00, for the QuikRead Go Strep A test kit, whereas estimates provided in the manufacturer submission ranged from 0.95, for Biopanda Reagents' Strep A Rapid Test cassette, to 0.98, for nal von minden GmbH's NADAL Strep A test. A similar trend in specificity is observed, with the manufacturers' estimates being generally much higher than estimates based on published data. Thus, the source of test accuracy data is likely to be an important driver of cost-effectiveness. The economic models presented here, which are based solely on manufacturers' test accuracy data with no peer-reviewed published data, are likely to overestimate test accuracy and, therefore, the results of these models cannot be reliably interpreted.

Prevalence of group A streptococcal infection in the modelled population

Data on the adult prevalence of strep A in the UK were available in one study out of the 38 published studies, abstracts and reports submitted by manufacturers to NICE included in our test accuracy effectiveness review. The study by Little *et al.*[6] from the review[85] (with additional data from the full HTA report[76]) found a prevalence rate of 34% (95% CI 31% to 38%) for pathogenic streptococcal infection among 204 out of 597 patients aged ≥ 5 years presenting in UK primary care settings. Of these infections, 136 (66.7%) were strep A. This gives a strep A prevalence rate of 22.7% (136/597). This study did not consecutively recruit patients, meaning that there may be bias in the sample, which could have affected the true prevalence rate. As there were no UK adult studies in secondary care, this estimate was used across both primary settings and secondary settings (*Table 22*).

There were no clear UK estimates for prevalence in children from the systematic review; a median value from three non-UK studies of children in primary care only was calculated.[24,46,52] The median value was 30.2%.

Treatment-related probabilities and complication rates

Treatment-related probabilities and complication rates following strep A that were used in the economic model are presented in *Table 23*. The proportion of patients attending repeat consultations for sore throat infections (used to inform calculation of treatment costs) was obtained from Little *et al.*[86] In this large cohort study of UK patients presenting in primary care with a sore throat, a total of 889 (14.2%) repeat consultations for new or resolved symptoms were reported among 13,288 adults and adolescents.

In base-case models, the probability of commencing antibiotic treatment given a positive clinical score (defined as Centor score of ≥ 3 points) in the usual-care arm or a positive clinical score and test result in the intervention arm was set to 1 based on the prescribing behaviour of GPs reported in the PRISM trial.[6] The probability of a delayed prescription given a negative clinical score (defined as Centor score of < 3 points in the base case) was set to 0.51 based on data suggesting that 91 out of 178 patients in the clinical score arm of the PRISM trial with a FeverPAIN score of < 4 points were offered a delayed prescription,[6] with the assumption that a Centor score of < 3 points is equivalent to a FeverPAIN score of < 4 points. The probability of a delayed prescription given a negative test was set to 0.273 based on the PRISM data (48/174 patients in the clinical score plus test arm were given a delayed prescription). The probability of antibiotic use among those receiving a delayed prescription was set to 0.46 based on PRISM data showing reported antibiotic use among the 75 out of 164 patients in the control arm who were offered delayed prescription.

TABLE 22 Prevalence of strep A by setting and population

Systematic review data			Estimate used in model			
Patient population and clinical settings	Number of studies	Median prevalence, % (range)	Central estimate	SE	Distribution	Source
Adults						
Primary and secondary care	One[6]	22.6	0.226	0.051	Beta	Systematic review
Children						
Primary and secondary care	Three[3,46,52]	30.2 (26.3–34.1)	30.2	0.015	Beta	Systematic review

SE, standard error.

TABLE 23 Probabilities used in the economic model

Description of parameter	Mean	SE[a]	Distribution	Source (first author and year of publication)
General practice				
Proportion attending repeat GP consultation following strep A infection	0.142	0.007	Beta	Little 2013[86]
Antibiotic-prescribing probabilities				
Probability of antibiotic use: Centor score of ≥ 3 points or positive test (immediate prescription)	1			Little 2013[6]
Probability of antibiotic use: Centor score of < 3 points (delayed prescription, usual-care arm)	0.51	0.026	Beta	Little 2013[6]
Probability of antibiotic use: negative test (delayed prescription, intervention arm)	0.267	0.014	Beta	Little 2013[6]
Probability of antibiotic use: delayed prescription	0.46	0.023	Beta	Little 2013[6]
Complication rates following strep A infection				
Probability of complications: antibiotics (treated infection)	0.013	0.0005	Beta	Little 2013[86]
Probability of complications: no antibiotics (untreated infection)	0.015	0.0007	Beta	Little 2013[86]
Proportion of complications that are non-suppurative (i.e. rheumatic fever)	0.0001			Analyst assumption
Adverse effects of penicillin				
Penicillin-induced rash	0.02		Beta	Neuner 2003[78]
Penicillin-induced anaphylaxis/sepsis	0.0001		Beta	Neuner 2003[78]

SE, standard error.
a SE derived assuming upper and lower bound equals to 10% of mean/central estimate.

Complications for treated (i.e. antibiotics given) and untreated (no antibiotics given) strep A infections were also estimated based on another Little *et al.*[86] study: 78 and 75 complications (quinsy, sinusitis, otitis media and cellulitis) were reported among 5932 treated and 4974 untreated individuals, generating a complication rate of 1.3% and 1.5%, respectively. As this study did not report rates for rare but important non-suppurative sequalae of strep A sore throat, such as acute rheumatic fever,[82] we assumed that the majority of complications were suppurative in nature, with only a tiny proportion of patients (no more than 0.01%) going on to develop non-suppurative sequelae. The impact of this assumption on the cost-effectiveness estimates was assessed by halving and doubling it in sensitivity analyses. We assumed that 2% of patients who were prescribed antibiotics (100% of those prescribed immediate antibiotics and 46% of those prescribed delayed antibiotics) will go on to develop penicillin-induced rash and 0.1% will develop penicillin-induced anaphylaxis/sepsis based on estimates reported in a previous economic evaluation of diagnostic and treatment strategies for adults with streptococcal pharyngitis.[78] Sensitivity analysis explored the impact of halving and doubling complications associated with penicillin use on the base-case cost-effectiveness.

Health utility and estimation of quality-adjusted life-year gains

Table 24 presents estimates of health utilities used to inform the economic model. A mean baseline utility of 0.863, equal to the mean utility norm for the general UK adult population,[87] was assumed for the modelled adult population treated in primary and secondary care. For the child population models, we assume a mean utility of 0.94, equivalent to the mean UK utility norm for the aged < 25 years population,[87] the closest age group to children. Utility decrements associated with strep A and related complications, such as development of peritonsillar abscess, rheumatic fever and anaphylactic

TABLE 24 Utilities

Utility/disutility	Mean	SE	Distribution	Source (first author and year of publication)
Baseline (UK population norm, adults)	0.863	0.044	Beta	Kind 1998[87]
Baseline (UK population norm, children)	0.94	0.048	Beta	Kind 1998[87]
Utility decrement associated with untreated infection	0.000685	0.00005	Beta	Neuner 2003[78]
Utility decrement associated with treated infection	0.000411	0.00003	Beta	Neuner 2003[78]
Utility decrement associated with penicillin-induced rash	0.0017	0.0001	Beta	Neuner 2003[78]
Utility decrement associated with abscess	0.0137	0.0007	Beta	Neuner 2003[78]
Utility decrement associated with penicillin-induced anaphylaxis (sepsis)	0.025	0.0013	Beta	Neuner 2003[78]
Utility decrement associated with rheumatic fever	0.209	0.011	Beta	Neuner 2003[78]

SE, standard error.

complications of penicillin, were obtained from previously published economic evaluations of diagnostic and management strategies for adults with pharyngitis.[78,79] The two studies[78,79] reported losses of 0.15 and 0.25 in quality-adjusted life-days for treated and untreated sore throat infections, and related complications, such as acute rheumatic fever, penicillin-induced anaphylaxis (sepsis), peritonsillar abscess and penicillin-induced rash, were associated with the greatest health impact, with estimates of 76.5, 9, 5 and 0.65 in quality-adjusted life-days lost, respectively. These estimates translate into utility decrements of 0.000411 (0.15/365) and 0.000685 (0.25/365) for treated and untreated strep A infection, respectively, 0.00178 (0.65/365) for penicillin-induced rash, 0.0037 (5/365) for peritonsillar abscess, 0.025 (9/365) for penicillin-induced sepsis and 0.209 (76.5/365) for rheumatic fever. QALYs were calculated at the end of each pathway in the model by subtracting from the baseline utility of 0.86 (or 0.94 for the child model) the utility decrements associated with all outcomes that occur in the modelled pathway (assuming that utility decrements are additive) weighted by modelled time horizon in years (i.e. 365/365 for the 1-year base-case time horizon). Disutility associated with unwanted effects of penicillin (rash and anaphylaxis) was added to care pathways associated with treated infection (immediate or delayed antibiotic use) weighted by the respective event probability (0.02 for penicillin-induced rash and 0.0001 for anaphylactic reaction). For example, the total number of QALYs accrued from uncomplicated strep A infection with complete resolution following immediate antibiotic treatment would be equal to (0.86 – 0.000410959 – 0.00003425 – 0.00000247) × 1 = 0.859552 QALYs over the 1-year time horizon considered in the base-case analysis for adults. Similarly, if this infection had resulted in a subsequent complication (e.g. an abscess), then the total QALY estimate would be slightly lower, at (0.86 – 0.000410959 – 0.01369863 – 0.00003425 – 0.00000247) × 1 = 0.84584.

Health and social care costs

Cost of tests

Table 25 presents the unit cost for each point-of-care test and estimates of resource use in terms of the additional GP time required to administer and process the test results. Cost data were available for 14 (66.7%) of the 21 tests considered in the NICE scope. The majority of the costs were provided by the manufacturers (submitted directly to NICE in response to a request for information) and ranged from £0.64 per test for Biopanda Reagents' Strep A Rapid Test strip to £64.63 (2017/18 prices) for the cobas Liat Strep A Assay supplied by Roche Diagnostics. Unit costs for Abbott Laboratories' Clearview Exact Strep A tests were obtained from the NHS supply chain catalogue at £1.92 per test for the Clearview Strep A dipstick – test strip and £2.72 for the cassette version.[88] The duration of additional GP time for processing test results was estimated based on information provided in the manufacturer

TABLE 25 Test costs

Test ID	Test name	Cost (£)	Test process time (minutes)	Source
1	Clearview Exact Strep A cassette (Abbott Laboratories)	2.72	5	*NHS Supply chain catalogue* (National Product Code = HHH2552)[88]
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	1.92	5	Medisave UK Ltd[89]
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)			Test cost not available
4	Strep A Rapid Test – cassette (Biopanda Reagents)	0.82	5	Manufacturer's submission[a]
5	Strep A Rapid Test – test strip (Biopanda Reagents)	0.64	5	Manufacturer's submission[a]
6	NADAL Strep A – test strip (nal von minden GmbH)	1.20	5	Manufacturer's submission[a]
7	NADAL Strep A – cassette (nal von minden GmbH)	1.40	5	Manufacturer's submission[a]
8	NADAL Strep A plus – cassette (nal von minden GmbH)	1.50	5	Manufacturer's submission[a]
9	NADAL Strep A plus – test strip (nal von minden GmbH)	1.30	5	Manufacturer's submission[a]
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	1.96	5	Manufacturer's submission[a]
11	OSOM Strep A test – test strip (Sekisui Diagnostics)			Test cost not available
12	QuikRead Go Strep A test kit (Orion Diagnostica)	4.34	5	Manufacturer's submission[a]
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	2.70	5	Manufacturer's submission[a]
14	bioNexia Strep A plus – cassette (bioMérieux)			Test cost not available
15	bioNexia Strep A dipstick – test strip (bioMérieux)			Test cost not available
16	Biosynex Strep A – cassette (Biosynex)			Test cost not available
17	Sofia Strep A FIA (Quidel)			Test cost not available
18	Alere i Strep A (Abbott Laboratories)			Test cost not available
19	Alere i Strep A 2 (Abbott Laboratories)	22.94	5	Test cost not available
20	cobas Liat Strep A Assay (Roche Diagnostics)	64.63	6	Manufacturer's submission[a]
21	Xpert Xpress Strep A (Cepheid)	4.25	12	Manufacturer's submission[a]

a Submitted directly to NICE in response to a request for information.

submission and ranged from 5 to 12 minutes. Costs associated with additional GP time for processing test results are included in the base-case analysis. The costs of confirmatory swab culture following a negative test result are calculated as part of the costs associated with modelled pathways in the intervention arm except for the Alere TestPack +Plus Strep A – cassette (Abbott Laboratories), Alere i Strep A 2 (Abbott Laboratories), cobas Liat Strep A Assay (Roche Diagnostics) and all five NADAL tests supplied by nal von minden GmbH. Details of costing methods are given in the next section.

Treatment costs

Unit costs of health-care service use associated with modelled care pathways are summarised in *Table 26*. As described in *Model structure*, the base-case models incorporate three treatment options for patients presenting with suspected strep A infection in primary care and secondary care settings: immediate antibiotics (option 1), delayed antibiotics with reported use (option 2) and delayed antibiotics that have not been used or no antibiotics offered (option 3). All three options account for

TABLE 26 Treatment costs (2017/18 price year)

Treatment costs	Mean cost (£)	SE (£)	Distribution	Source
GP consultation (9.22 minutes)	37.4	1.91	Gamma	PSSRU unit costs 2017[90]
Antibiotic (phenoxymethylpenicillin 250 mg, 28-tablet pack)	0.91	0.046	Gamma	BNF 74 (2017)[91]
Pain relief (paracetamol 500 mg, 32-tablet pack)	0.74	0.037	Gamma	BNF 74 (2017)[91]
Throat culture (swab)	8.00	0.41	Gamma	*NHS Reference Costs 2017/18*[92]
Penicillin-induced rash [switch to 500 mg of erythromycin (Erythrocin®; ADVANZ Pharma, London, UK)]	10.00	0.51	Gamma	BNF 74 (2017)[91]
Treatment costs: sepsis	1744.64	89.01	Gamma	Derived from data reported in Hex *et al.* (2017)[93]
Treatment modality costs (assumptions)				
Treatment option 1 (usual-care and intervention arms) and option 2 (usual-care arm): assume immediate/delayed antibiotics (£0.91) at initial consultation (£37.43); 14.2% reconsultations during which patients get paracetamol (£5.42) plus weighted treatment costs penicillin side effects (£1.12 per patient)	44.89			Derived from other treatment costs
Treatment option 2 (intervention arm): assume that antibiotics (£0.91) given at initial consultation (£37.43); 14.2% reconsultations during which patients get paracetamol (£5.42), weighted treatment costs penicillin side effects (£1.12 per patient) and confirmatory culture (£8)	52.89			Derived from other treatment costs
Treatment option 3 (usual-care arm): assume paracetamol (£0.74) at initial consultation (£37.43) and delayed antibiotic use among the 14.2% attending repeat consultation (£5.60)	43.78			Derived from other treatment costs
Treatment option 3 (intervention arm): assume paracetamol (£0.74) at initial consultation (£37.43), delayed antibiotic use among the 14.2% attending repeat consultation (£5.60) and confirmatory throat culture (£8)	51.77			Derived from other treatment costs
Complication of strep A costs				
Treatment costs: abscess	1571.28	80	Gamma	*NHS Reference Costs 2017/18*[92] [tonsillectomy, 19 years and over (HRG code CA60A)]
Treatment costs: acute rheumatic fever	1772.44	90.43	Gamma	*NHS Reference Costs 2017/18*[92] [other acquired cardiac conditions with a CC score of 6–8 (HRG code EB14C)]

BNF, *British National Formulary*; CC, complications and comorbidities; HRG, Healthcare Resource Group; PSSRU, Personal Social Services Research Unit; SE, standard error.

repeat GP consultations at 14.2%[6] over the modelled time horizon, with a typical GP consultation lasting 9.22 minutes at an average cost of £4.02 per minute[90] and pain relief (500 mg of paracetamol) costing £0.74 per 32-tablet pack,[91] but the options differed in the way that antibiotics are prescribed.

Under options 1 and 2, patients incur a cost of antibiotics at £0.91 per treatment course (phenoxymethylpenicillin 250 mg, 28-tablet pack)[91] and costs associated with managing adverse effects of penicillin: penicillin-induced rash [assumed to be seen by GP at additional expense (£4.02 per minute) and switched to erythromycin 500 mg at £10 per treatment course[91] weighted by 0.02, the probability of a rash] and penicillin-induced anaphylaxis [estimated at £1744 based on data reported in a 2017 cost of sepsis study[93] (see *Table 26*) weighted by 0.0001, the probability of sepsis].[78] No costs associated with antibiotic use are included under option 3 (delayed antibiotics prescription given but not used); however, we assume that 14.2% of patients attended a repeat consultation[86] and will use the delayed antibiotics prescription under this option.

Confirmatory swab culture costing £8[92] was added to options 2 and 3 for patients with a negative test result (intervention only) but not to option 1, as patients with a positive test result receive immediate antibiotics. On average, the estimated treatment costs based on these assumptions and a repeat consultation rate of 14.2% were £44.89 (option 1: intervention and usual-care arms; option 2: usual-care arm), £52.89 (option 2: intervention arm including confirmatory culture costs), £43.78 (option 3: usual-care arm) and £51.77 (option 3: intervention arm including confirmatory culture costs) (see *Table 26*).

The cost of sepsis was estimated to be £1744 based on data reported in a study,[93] which estimated that 93,973 adults would need treatment for sepsis in UK hospitals, at an annual total cost of £163,949,055 (see *Table 26*). The cost of treating strep A-related abscess was estimated at £1571 based on the NHS reference cost for a tonsillectomy in adults aged ≥ 19 years with a Healthcare Resource Group code of CA60A.[92] The cost of treating acute rheumatic fever was estimated at £1772.44 based on the NHS reference cost for other acquired cardiac conditions with a CC (complications and comorbidities) score of 6–8 and a Healthcare Resource Group code EB14C.[92]

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to explore the impact of parameter uncertainty on base-case cost-effectiveness of point-of-care testing for strep A infection. The PSA was implemented via Monte Carlo simulations involving 1000 draws for all model inputs except for the acquisition costs of the tests, which were entered as deterministic values. This enabled us to simulate 1000 replicates of the base-case ICER (displayed on cost-effectiveness planes) and calculate the probability of cost-effectiveness at threshold values ranging from £0 to £100,000 per QALY gained (CEACs). The sensitivity and specificity of the clinical scoring algorithm and individual point-of-care tests were assumed to be drawn from separate normal distributions on the logit scale, as the relatively small number of studies reporting test-specific accuracy data precluded joint synthesis of sensitivity and specificity and estimation of the between-study correlation (see *Tables 20* and *21*). Prevalence, probabilities and utility values (see *Tables 22–24*) were assumed to be drawn from a beta distribution reflecting scale of measurement for quantities constrained to lie in the interval 0–1. Costs were assigned a gamma distribution to reflect the distribution of health-care costs, which cannot be less than 0 and are typically highly skewed to the right due to a smaller number of individuals incurring high costs. Generally, the uncertainty surrounding input parameters [standard errors (SEs) and CIs] was not available; therefore, we assumed a 10% of the mean as equivalent to lower and upper 95% confidence limits and calculated the SEs assuming approximate normal distribution.

Base-case analyses

The main base-case model was based on the adult population in a primary care setting. This model was then adapted for adults in a secondary care setting, for children in a primary care setting and for children in a secondary care setting.

Adult primary care model: base-case analysis results

The base-case cost-effectiveness results for adults treated in primary care are presented in *Table 27* for 14 of the 21 tests for which test accuracy and cost data were available. The rate at which incremental QALYs accrued over the 1-year modelled time horizon was small; thus, estimates of simulated costs and QALYs were multiplied by 1000 to aid clarity in presentation of incremental estimates in the result tables and texts. The mean simulated costs under base-case assumptions were £49,147 per 1000 individuals treated in primary care under usual-care practice, and ranged from £54,394 per 1000 individuals in the test group using the NADAL Strep A – test strip (nal von minden GmbH) to £71,277 per 1000 individuals using the cobas Liat Strep A Assay (Roche Diagnostics). The corresponding estimated mean QALYs were 859.825 per 1000 individuals under usual-care practice, and ranged between 859.821 QALYs per 1000 individuals in the intervention group using Abbott Laboratories' Clearview Exact Strep A cassette or test strip to 859.829 QALYs per 1000 individuals using Cepheid's Xpert Xpress Strep A tests. In terms of incremental cost-effectiveness, the base-case estimates suggest that usual care was cheaper and generated marginally more QALYs than (and therefore dominated) the cassette and strip versions of Abbott Laboratories' Clearview Exact Strep A test. ICERs for the remaining 12 tests suggest that testing was more costly and more effective than usual care, with ICERs ranging from £1,353,677 per QALY gained for nal von minden GmbH's NADAL Strep A test strip to £6,059,081 per QALY gained for Roche Diagnostics' cobas Liat Strep A Assay compared with usual care.

Adult primary care model: probabilistic sensitivity analyses

Table 28 presents probabilistic estimates for adults presenting in primary care. The probabilistic estimates were very similar to the deterministic base-case results, with ICERs indicating that usual care dominated two (the Clearview Exact Strep A cassette and the Clearview Exact Strep A dipstick – test strip supplied by Abbott Laboratories) of the 14 tests considered in the economic modelling. Base-case probabilistic ICERs for the remaining 11 tests ranged from £1,495,402 per QALY gained for NADAL Strep A plus – test strip supplied by nal von minden GmbH to £6,498,666 per QALY gained for cobas Liat Strep A Assay supplied by Roche Diagnostics. The probability for testing to be cost-effective was zero at a cost-effectiveness threshold of £20,000 per QALY gained under the base-case assumptions and model inputs regardless of the point-of-care test used in comparison with usual care.

Adult primary care model: exploratory sensitivity analyses

Exploratory analyses were conducted to test the robustness of the economic base-case estimates for adults presenting in primary care with suspected strep A. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented for only those tests for which the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care). See *Appendix 9* for more detail.

Adult secondary care model: base-case analysis results

The primary care adult model (see *Model structure*) was adapted to model adult patients presenting with suspected strep A infection in secondary care settings (urgent care/walk-in centres and emergency departments). The modelled pathways remain the same as the adult primary care model depicted in *Figures 12–14*. Sensitivity and specificity of the clinical score at the specified Centor score of ≥ 3 points for a positive strep A infection were left unchanged as in the adult primary care model (see *Table 20*), as were the modelled pathway probabilities (see *Table 23*) and health state utility values (see *Table 24*). However, the two models differ in the way that treatment and testing costs are calculated. The secondary care model assumes that the care pathways associated with suspected cases of strep A infections are presenting for the first time in secondary care and have not received any treatment in primary care. The cost of the initial GP consultation included in the adult primary care model is, therefore, excluded from the cost. However, the model does account for patients attending a GP consultation (and the associated costs) following hospital discharge at a rate equal to the proportion attending repeat GP consultations in the primary care model (14.2% based on figures reported in Little *et al.*[86]). In addition, we assume that point-of-care testing within secondary care settings can be carried out within the standard allocated time

TABLE 27 Adult primary care model: base-case cost-effectiveness results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 1000 individuals	Incremental cost (£) per 1000 individuals	Incremental QALYs per 1000 individuals	ICER (£) vs. usual care
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	49,147	859.82458955	0	0.0000000	–
1	Clearview Exact Strep A cassette (Abbott Laboratories)	56,180	859.82063008	7033	−0.0039595	Dominated
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	55,980	859.82063008	6833	−0.0039595	Dominated
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)					
4	Strep A Rapid Test – cassette (Biopanda Reagents)	55,442	859.82769587	6295	0.0031063	2,026,496
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	55,397	859.82769587	6250	0.0031063	2,012,006
6	NADAL Strep A – test strip (nal von minden GmbH)	54,394	859.82846603	5248	0.0038765	1,353,677
7	NADAL Strep A – cassette (nal von minden GmbH)	54,444	859.82846603	5298	0.0038765	1,366,577
8	NADAL Strep A plus – cassette (nal von minden GmbH)	54,469	859.82846603	5323	0.0038765	1,373,029
9	NADAL Strep A plus – test strip (nal von minden GmbH)	54,419	859.82846603	5273	0.0038765	1,360,126
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	54,584	859.82846603	5438	0.0038765	1,402,700
11	OSOM Strep A test – test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	56,083	859.82810269	6936	0.0035131	1,974,319
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	54,781	859.82751669	5634	0.0029271	1,924,717
14	bioNexia Strep A plus – cassette (bioMérieux)					
15	bioNexia Strep A dipstick – test strip (bioMérieux)					
16	Biosynex Strep A – cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	Alere i Strep A (Abbott Laboratories)					
19	Alere i Strep A 2 (Abbott Laboratories)	59,837	859.82824206	10,691	0.0036525	2,926,915
20	cobas Liat Strep A Assay (Roche Diagnostics)	71,277	859.82824206	22,131	0.0036525	6,059,081
21	Xpert Xpress Strep A (Cepheid)	63,323	859.82854357	14,177	0.0039540	3,585,436

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip not available; assumed that the strip has the same test accuracy as the cassette version of the test.

Note

Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available.

TABLE 28 Adult primary care model: PSA results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 1000 individuals	Incremental costs (£) per 1000 individuals	Incremental QALYs per 1000 individuals	ICER (£) vs. usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	49,295	861.0209476	0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott Laboratories)	56,387	861.0168718	7092	−0.0040758	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	56,183	861.0169652	6888	−0.0039824	Dominated	0
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)						
4	Strep A Rapid Test – cassette (Biopanda Reagents)	55,636	861.0239908	6341	0.0030432	2,083,738	0
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	55,590	861.0239997	6295	0.0030521	2,062,510	0
6	NADAL Strep A – test strip (nal von minden GmbH)	54,582	861.0244537	5288	0.0035061	1,508,134	0
7	NADAL Strep A – cassette (nal von minden GmbH)	54,634	861.0243797	5339	0.0034321	1,555,613	0
8	NADAL Strep A plus – cassette (nal von minden GmbH)	54,658	861.0244709	5363	0.0035233	1,522,258	0
9	NADAL Strep A plus – test strip (nal von minden GmbH)	54,607	861.0245002	5313	0.0035526	1,495,402	0
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	54,775	861.0244341	5480	0.0034865	1,571,686	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	56,273	861.0244144	6978	0.0034668	2,012,942	0
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	54,968	861.0237881	5673	0.0028405	1,997,326	0
14	bioNexia Strep A plus – cassette (bioMérieux)						
15	bioNexia Strep A dipstick – test strip (bioMérieux)						
16	Biosynex Strep A – cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	Alere i Strep A (Abbott Laboratories)						
19	Alere i Strep A 2 (Abbott Laboratories)	60,056	861.0244146	10,761	0.0034670	3,103,806	0
20	cobas Liat Strep A Assay (Roche Diagnostics)	71,565	861.0243746	22,271	0.0034270	6,498,666	0
21	Xpert Xpress Strep A (Cepheid)	63,581	861.0248804	14,286	0.0039328	3,632,549	0

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip not available; assumed that the strip has the same test accuracy as the cassette version of the test.

for most hospital-based appointments, such that no additional time is required for administering and processing test results.

Test accuracy estimates were obtained from our systematic review and remained broadly the same as those used to inform the adult primary care model (see *Table 21*) except for three tests (OSOM Strep A test strip, QuikRead Go Strep A test kit and the Alere TestPack +Plus Strep A – cassette). *Table 29* presents test accuracy estimates used in the adult secondary care model for these three point-of-care tests. Estimates of sensitivity changed from 0.92 in primary care to 0.94 in secondary care for the OSOM Strep A test strip, from 1.00 in primary care to 0.87 in secondary care for the QuikRead Go Strep A test kit and from 0.95 in primary care to 0.90 in secondary care for the Alere TestPack +Plus Strep A – cassette. However, estimates of specificity for the three tests remain broadly unchanged across primary and secondary care settings.

Table 30 presents the cost-effectiveness results for adults in a secondary care setting. As with the adult primary care model, only 14 of the 21 tests that have test accuracy and costs data have been included in this analysis. The pattern and direction of cost-effectiveness in the secondary care adult model are similar to what has been observed in the adult primary care model, although the ICERs were generally lower in the secondary care model.

Two tests (Abbotts Laboratories' Clearview Exact Strep A cassette and Clearview Exact Strep A dipstick – test trip) generated fewer QALYs than usual care and produced ICERs indicating being dominated by usual care (i.e. were less effective and more costly). The remaining 12 tests all generated marginally more QALYs than usual care. The ICERs ranged from £44,184 per QALY gained for NADAL Strep A – test strip (nal von minden GmbH) to £12,700,432 per QALY gained for the QuikRead Go Strep A test kit supplied by Orion Diagnostica.

Adult secondary care model: probabilistic sensitivity analyses

Probabilistic results for the adult secondary care model mirrored the adult primary care PSA model. Results are shown in *Table 31*.

Adult secondary care model: exploratory sensitivity analyses

Exploratory analyses were conducted to test the robustness of the economic base-case estimates for adults presenting in secondary care with suspected strep A infection. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented for only those tests for which the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care). See *Appendix 10* for more detail.

TABLE 29 Adult secondary care model: test accuracy of point-of-care tests used in the economic model

Test name	Sensitivity (95% CI)	Specificity (95% CI)	Assumed distribution	Data source (first author and year of publication)
OSOM Strep A test – test strip (Sekisui Diagnostics)	0.94 (0.89 to 0.98)	0.95 (0.91 to 0.98)	Normal (logit)	Five studies (Bura 2017,[36] Llor 2009,[44] Llor 2011,[45] Rogo 2011[49] and Weinzierl 2018[54])
QuikRead Go Strep A test kit (Orion Diagnostica)	0.87 (0.78 to 0.95)	0.78 (0.71 to 0.85)	Normal (logit)	Two studies (Azrad 2019[34] and Stefaniuk 2017[52])
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	0.90 (0.86 to 0.94)	0.95 (0.92 to 0.96)	Normal (logit)	One study (Rosenberg 2002[50]) and one abstract (Valverde 2018[58])

Only tests with secondary care accuracy estimates that are different from those used to inform the adult primary care model are presented in this table.

TABLE 30 Adult secondary care model: base-case cost-effectiveness results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 1000 individuals	Incremental cost (£) per 1000 individuals	Incremental QALYs per 1000 individuals	ICER (£) vs. usual care
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	49,147	859.82458955	0	0.0000000	
1	Clearview Exact Strep A cassette (Abbott Laboratories)	51,103	859.82063008	1957	−0.0039595	Dominated
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	50,903	859.82063008	1757	−0.0039595	Dominated
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)					
4	Strep A Rapid Test – cassette (Biopanda Reagents)	50,365	859.82769587	1219	0.0031063	392,342
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	50,320	859.82769587	1174	0.0031063	377,852
6	NADAL Strep A – test strip (nal von minden GmbH)	49,318	859.82846603	171	0.0038765	44,184
7	NADAL Strep A – cassette (nal von minden GmbH)	49,368	859.82846603	221	0.0038765	57,085
8	NADAL Strep A plus – cassette (nal von minden GmbH)	49,393	859.82846603	246	0.0038765	63,537
9	NADAL Strep A plus – test strip (nal von minden GmbH)	49,343	859.82846603	196	0.0038765	50,636
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	49,508	859.82846603	361	0.0038765	93,211
11	OSOM Strep A test – test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	51,136	859.82474622	1990	0.0001567	12,700,432
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	49,713	859.82627789	566	0.0016883	335,358
14	bioNexia Strep A plus – cassette (bioMérieux)					
15	bioNexia Strep A dipstick – test strip (bioMérieux)					
16	Biosynex Strep A – cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	Alere i Strep A (Abbott Laboratories)					
19	Alere i Strep A 2 (Abbott Laboratories)	54,761	859.82824206	5614	0.0036525	1,537,126
20	cobas Liat Strep A Assay (Roche Diagnostics)	65,186	859.82824206	16,039	0.0036525	4,391,332
21	Xpert Xpress Strep A (Cepheid)	51,141	859.82854357	1994	0.0039540	504,287

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip were not available; assumed that the strip has the same test accuracy as the cassette version of the test.

Note

Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available.

TABLE 31 Adult secondary care model: PSA results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 1000 individuals	Incremental cost (£) per 1000 individuals	Incremental QALYs per 1000 individuals	ICER (£) vs. usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	49,182	860.0288998	0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott Laboratories)	51,128	860.0249274	1947	−0.0039724	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	50,924	860.024949	1743	−0.0039508	Dominated	0
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)						
4	Strep A Rapid Test – cassette (Biopanda Reagents)	50,416	860.0319673	1234	0.0030675	402,358	0
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	50,370	860.0319912	1188	0.0030914	384,360	0
6	NADAL Strep A – test strip (nal von minden GmbH)	49,358	860.0323456	177	0.0034458	51,324	0
7	NADAL Strep A – cassette (nal von minden GmbH)	49,408	860.0324406	226	0.0035408	63,963	0
8	NADAL Strep A plus – cassette (nal von minden GmbH)	49,433	860.0324859	251	0.0035860	70,042	0
9	NADAL Strep A plus – test strip (nal von minden GmbH)	49,382	860.032473	201	0.0035731	56,186	0
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	49,550	860.0324781	368	0.0035783	102,876	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	51,187	860.0289465	2005	0.0000467	42,951,995	0
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	49,754	860.0306084	573	0.0017086	335,098	0
14	bioNexia Strep A plus – cassette (bioMérieux)						
15	bioNexia Strep A dipstick – test strip (bioMérieux)						
16	Biosynex Strep A – cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	Alere i Strep A (Abbott Laboratories)						
19	Alere i Strep A 2 (Abbott Laboratories)	54,870	860.0323487	5688	0.0034488	1,649,300	0
20	cobas Liat Strep A Assay (Roche Diagnostics)	65,430	860.0322608	16,248	0.0033610	4,834,450	0
21	Xpert Xpress Strep A (Cepheid)	51,204	860.0328714	2022	0.0039715	509,167	0

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip were not available; assumed that the strip has the same test accuracy as the cassette version of the test.

Children's primary care model: base-case results

The primary care adult model (see *Model structure*) was adapted to model children presenting with suspected strep A infection in a primary care setting. The modelled pathways remain the same as the adult primary care model depicted in *Figures 12–14*. The prevalence of strep A changed from 22.6% in the adult primary care model to 30.2%, the median prevalence in our systematic review of test accuracy studies among children in primary care settings (see *Table 22*). Sensitivity and specificity of the clinical score at the specified Centor score of ≥ 3 points for a positive strep A infection were left unchanged (see estimates displayed in *Table 20*), as well as the modelled pathway probabilities (see *Table 23*) and health-state utility values (see *Table 24*). Test accuracy estimates were obtained from our systematic review and remained broadly the same as those used to inform the adults in primary care model (see *Table 21*) except for five tests (BD Veritor Plus system group A Strep Assay – cassette supplied by Becton Dickinson, OSOM Strep A test – test strip supplied by Sekisui Diagnostics, QuikRead Go Strep A test kit by Orion Diagnostica and Alere TestPack +Plus Strep A – cassette and Alere i Strep A both supplied by Abbott Laboratories). See *Table 21* for further details.

Treatment costs for peritonsillar abscess and related complications of strep A infection in children were estimated at £1420.50 (tonsillectomy, aged ≤ 18 years, with Healthcare Resource Group code CA60B);[92] this is slightly lower than the estimate used in the adult primary care model for these complications (£1571.28 for tonsillectomy, aged ≥ 19 years, with Healthcare Resource Group code CA60A).[92] Treatment costs for penicillin-induced rash were left unchanged as in the adult models at £10 (assuming that treatment switched to another antibiotic, e.g. 500 mg of erythromycin), and anaphylaxis was £1744.64.[93]

Overall, 14 of the 21 tests were included in the child primary care model. Cost-effectiveness estimates for these tests compared with usual care are presented in *Table 32*. Simulated mean costs and QALYs were multiplied by 1000 to aid clarity in presentation because of the small number of QALYs accrued over a 1-year time horizon. The base-case cost-effectiveness for children presenting in primary care largely mirrored that for the adult population. However, because of the slightly higher prevalence of strep A in children (30.2%) than in adults (22.6%), simulated costs over the 1-year time horizon were generally higher in the children's model than those in the adult primary care model.

The mean costs simulated under base-case assumptions were £50,185 (£49,147 in the adult primary care model) per 1000 children treated in primary care under usual-care practice and ranged from £55,952 (£54,394 in the adult primary care model) per 1000 children for NADAL Strep A – test strip (nal von minden GmbH) to £74,425 (£71,277 adult primary care model) per 1000 children treated in primary care for cobas Liat Strep A Assay supplied by Roche Diagnostics. Simulated QALYs were also higher for children treated in primary care than for adults because of the higher baseline utility in children (0.94), compared with a utility norm of 0.863 for adults in the UK. Simulated mean QALYs were 939.7702 (859.8246 in the adult primary care model) for children treated in primary care under usual-care practice and ranged from 939.7631 (859.8206 adult primary care model) for Abbott Laboratories' Clearview Exact Strep A test cassette and strip to 939.7737 (859.8285 in the adult primary care model) for the other tests.

In terms of incremental cost-effectiveness, the base-case estimates suggest that usual care was cheaper and generated marginally more QALYs than (and therefore dominated) the QuikRead Go Strep A test kit (Orion Diagnostica), the cassette and strip versions of the Clearview Exact Strep A test cassette supplied by Abbott Laboratories and the Alere TestPack +Plus Strep A – cassette also supplied by Abbott Laboratories. ICERs for the remaining 10 tests suggest that testing for children in primary care under base-case assumptions produced ICERs ranging from £1,762,306 per QALY gained for NADAL Strep A – test strip (nal von minden GmbH) to £7,893,857 per QALY gained for the Xpert Xpress Strep A by Cepheid compared with usual care.

Children's primary care model: probabilistic sensitivity analyses

Probabilistic results for the children's primary care model are shown in *Table 33* and are in line with the deterministic results for the children's primary care model.

TABLE 32 Children's primary care model: base-case cost-effectiveness results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 10,000 individuals	Incremental cost (£) per 10,000 individuals	Incremental QALYs per 10,000 individuals	ICER (£) vs. usual care
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	50,185	939.77019917	0	0.0000000	
1	Clearview Exact Strep A cassette (Abbott Laboratories)	57,773	939.76305927	7588	−0.0071399	Dominated
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	57,554	939.76305927	7369	−0.0071399	Dominated
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)					
4	Strep A Rapid Test – cassette (Biopanda Reagents)	56,899	939.77244279	6715	0.0022436	2,992,743
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	56,850	939.77244279	6665	0.0022436	2,970,792
6	NADAL Strep A – test strip (nal von minden GmbH)	55,952	939.77347194	5768	0.0032728	1,762,306
7	NADAL Strep A – cassette (nal von minden GmbH)	56,007	939.77347194	5822	0.0032728	1,779,026
8	NADAL Strep A plus – cassette (nal von minden GmbH)	56,035	939.77347194	5850	0.0032728	1,787,386
9	NADAL Strep A plus – test strip (nal von minden GmbH)	55,980	939.77347194	5795	0.0032728	1,770,666
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	56,160	939.77347194	5976	0.0032728	1,825,846
11	OSOM Strep A test – test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	58,012	939.76701428	7827	−0.0031849	Dominated
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	56,389	939.76939575	6204	−0.0008034	Dominated
14	bioNexia Strep A plus – cassette (bioMérieux)					
15	bioNexia Strep A dipstick – test strip (bioMérieux)					
16	Biosynex Strep A – cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	Alere i Strep A (Abbott Laboratories)					
19	Alere i Strep A 2 (Abbott Laboratories)	61,907	939.77326996	11,722	0.0030708	3,817,336
20	cobas Liat Strep A Assay (Roche Diagnostics)	74,425	939.77326996	24,240	0.0030708	7,893,857
21	Xpert Xpress Strep A (Cepheid)	65,521	939.77368771	15,336	0.0034885	4,396,205

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip were not available; assumed that the strip has the same test accuracy as the cassette version of the test.

Note

Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available.

TABLE 33 Children's primary care model: PSA results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 1000 individuals	Incremental cost (£) per 1000 individuals	Incremental QALYs per 1000 individuals	ICER (£) vs. usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	50,204	940.0932608	0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott Laboratories)	57,887	940.0862286	7683	−0.0070321	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	57,668	940.0862027	7464	−0.0070580	Dominated	0
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)						
4	Strep A Rapid Test – cassette (Biopanda Reagents)	57,016	940.0954301	6812	0.0021694	3,140,063	0
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	56,964	940.0955022	6760	0.0022415	3,015,747	0
6	NADAL Strep A – test strip (nal von minden GmbH)	56,046	940.0960689	5841	0.0028082	2,080,115	0
7	NADAL Strep A – cassette (nal von minden GmbH)	56,101	940.0960859	5897	0.0028251	2,087,246	0
8	NADAL Strep A plus – cassette (nal von minden GmbH)	56,128	940.0961173	5924	0.0028566	2,073,823	0
9	NADAL Strep A plus – test strip (nal von minden GmbH)	56,073	940.0961534	5869	0.0028927	2,028,782	0
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	56,255	940.0961639	6051	0.0029031	2,084,258	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	58,149	940.0895996	7944	−0.0036612	Dominated	0
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	56,482	940.0924978	6278	−0.0007629	Dominated	0
14	bioNexia Strep A plus – cassette (bioMérieux)						
15	bioNexia Strep A dipstick – test strip (bioMérieux)						
16	Biosynex Strep A – cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	Alere i Strep A (Abbott Laboratories)						
19	Alere i Strep A 2 (Abbott Laboratories)	62,058	940.0960474	11,854	0.0027866	4,253,800	0
20	cobas Liat Strep A Assay (Roche Diagnostics)	74,704	940.0960301	24,500	0.0027693	8,846,880	0
21	Xpert Xpress Strep A (Cepheid)	65,741	940.096771	15,536	0.0035102	4,426,070	0

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip were not available; assumed that the strip has the same test accuracy as the cassette version of the test.

Children's primary care model: exploratory sensitivity analyses

Exploratory analyses were conducted to test the robustness of economic base-case estimates for children presenting in primary care with suspected strep A infection. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented for only those tests for which the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care). See *Appendix 11* for more detail.

Children in secondary care: base-case analysis results

The models for adults in secondary care (see *Adult secondary care model: base-case analysis results*) and children in primary care (see *Children's primary care model: base-case results*) were adapted to model suspected strep A infection among children in secondary care settings (urgent care/walk-in centres and emergency departments). The modelled pathways remain the same as depicted in *Figures 12–14*. The prevalence rate was maintained at 30.2%, as in the children's primary care model. Test accuracy estimates obtained from our systematic review remained broadly the same as those used to inform the primary care models except for six tests [BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson), OSOM Strep A test – test strip (Sekisui Diagnostics), QuikRead Go Strep A test kit (Orion Diagnostica), Alere TestPack +Plus Strep A – cassette (Abbott Laboratories), Alere i Strep A (Abbott Laboratories) and Xpert Xpress Strep A (Cepheid)]. *Table 34* presents test accuracy estimates used in the children's secondary care model for these tests.

Table 35 presents cost-effectiveness estimates for children treated in secondary care. As with the adult primary care model, only 14 of the 21 tests that have test accuracy and costs data are included in this analysis. The base-case estimates suggest that usual care was cheaper and generated marginally more QALYs than (and therefore dominated) four tests [Clearview Exact Strep A cassette (Abbott Laboratories), Clearview Exact Strep A dipstick – test strip (Abbott Laboratories), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)]. ICERs for the remaining tests suggest that testing was more costly and more effective than usual care, with ICERs ranging from £65,122 per QALY gained for the NADAL Strep A – test strip (nal von minden GmbH) to £5,723,279 per QALY gained for cobas Liat Strep A Assay (Roche Diagnostics) compared with usual care.

Children's secondary care model: probabilistic sensitivity analyses

Probabilistic results for the children's secondary care model mirrored the children primary care PSA model. Results are shown in *Table 36*.

TABLE 34 Children's secondary care model: test accuracy of point-of-care tests used in the economic model

Test name	Sensitivity (95% CI)	Specificity (95% CI)	Assumed distribution	Data source (first author and year)
OSOM Strep A test – test strip (Sekisui Diagnostics)	0.94 (0.89 to 0.98)	0.97 (0.95 to 0.99)	Normal (logit)	Two studies (Rogo 2011[49] and Weinzierl 2018[54])
QuikRead Go Strep A test kit (Orion Diagnostica)	0.87 (0.78 to 0.95)	0.78 (0.71 to 0.85)	Normal (logit)	Two studies (Azrad 2019[34] and Stefaniuk 2017[52])
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	0.77 (0.73 to 0.8)	0.97 (0.93 to 0.99)	Normal (logit)	Four studies (Kurtz 2000,[42] Lacroix 2018,[23] Penney 2016[48] and Santos 2003[51])

Only tests with secondary care accuracy estimates that are different from those used to inform the children's primary care model are presented here.

TABLE 35 Children's secondary care model: base-case cost-effectiveness results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 10,000 individuals	Incremental cost (£) per 10,000 individuals	Incremental QALYs per 10,000 individuals	ICER (£) vs. usual care
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	50,185	939.77019917	0	0.0000000	
1	Clearview Exact Strep A cassette (Abbott Laboratories)	52,219	939.76305927	2034	−0.0071399	Dominated
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	52,000	939.76305927	1815	−0.0071399	Dominated
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)					
4	Strep A Rapid Test – cassette (Biopanda Reagents)	51,345	939.77244279	1160	0.0022436	517,066
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	51,296	939.77244279	1111	0.0022436	495,115
6	NADAL Strep A – test strip (nal von minden GmbH)	50,398	939.77347194	213	0.0032728	65,122
7	NADAL Strep A – cassette (nal von minden GmbH)	50,453	939.77347194	268	0.0032728	81,845
8	NADAL Strep A plus – cassette (nal von minden GmbH)	50,480	939.77347194	295	0.0032728	90,205
9	NADAL Strep A plus – test strip (nal von minden GmbH)	50,425	939.77347194	240	0.0032728	73,482
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	50,606	939.77347194	421	0.0032728	128,662
11	OSOM Strep A test – test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	52,457	939.76701428	2273	−0.0031849	Dominated
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	50,834	939.76939575	649	−0.0008034	Dominated
14	bioNexia Strep A plus – cassette (bioMérieux)					
15	bioNexia Strep A dipstick – test strip (bioMérieux)					
16	Biosynex Strep A – cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	Alere i Strep A (Abbott Laboratories)					
19	Alere i Strep A 2 (Abbott Laboratories)	56,353	939.77326996	6168	0.0030708	2,008,522
20	cobas Liat Strep A Assay (Roche Diagnostics)	67,760	939.77326996	17,575	0.0030708	5,723,279
21	Xpert Xpress Strep A (Cepheid)	52,190	939.77368771	2006	0.0034885	574,900

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip were not available; assumed that the strip has the same test accuracy as the cassette version of the test.

Note

Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available.

TABLE 36 Children's secondary care model: PSA results

Test ID	Test name	Mean cost (£) per 1000 individuals	Mean QALYs per 1000 individuals	Incremental cost (£) per 1000 individuals	Incremental QALYs per 1000 individuals	ICER (£) vs. usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (clinical scoring based on Centor ≥ 3 points plus clinical assessment)	50,000	940.2967868	0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott Laboratories)	51,783	940.2897117	1783	−0.0070750	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	51,563	940.2897075	1563	−0.0070792	Dominated	0
3	BD Veritor Plus system group A Strep Assay – cassette (Becton Dickinson)						
4	Strep A Rapid Test – cassette (Biopanda Reagents)	51,138	940.2989313	1138	0.0021445	530,655	0
5	Strep A Rapid Test – test strip (Biopanda Reagents)[a]	51,088	940.2989679	1088	0.0021812	498,896	0
6	NADAL Strep A – test strip (nal von minden GmbH)	50,217	940.2996263	217	0.0028395	76,288	0
7	NADAL Strep A – cassette (nal von minden GmbH)	50,272	940.299611	272	0.0028243	96,309	0
8	NADAL Strep A plus – cassette (nal von minden GmbH)	50,299	940.2996798	299	0.0028931	103,485	0
9	NADAL Strep A plus – test strip (nal von minden GmbH)	50,245	940.2995732	245	0.0027865	87,781	0
10	NADAL Strep A scan test – cassette (nal von minden GmbH)	50,427	940.2995398	427	0.0027531	154,933	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	52,132	940.2930891	2132	−0.0036976	Dominated	0
13	Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	50,652	940.2959919	652	−0.0007948	Dominated	0
14	bioNexia Strep A plus – cassette (bioMérieux)						
15	bioNexia Strep A dipstick – test strip (bioMérieux)						
16	Biosynex Strep A – cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	Alere i Strep A (Abbott Laboratories)						
19	Alere i Strep A 2 (Abbott Laboratories)	56,210	940.2995831	6210	0.0027963	2,220,667	0
20	cobas Liat Strep A Assay (Roche Diagnostics)	67,693	940.2994655	17,693	0.0026787	6,605,137	0
21	Xpert Xpress Strep A (Cepheid)	52,023	940.3002769	2023	0.0034902	579,711	0

a Test accuracy data for Biopanda Reagents' Strep A Rapid Test – test strip were not available; assumed that the strip has the same test accuracy as the cassette version of the test.

Children's secondary care model: exploratory sensitivity analyses

Exploratory analyses were conducted to test the robustness of economic base-case estimates for children presenting in secondary care with suspected strep A infection. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented for only those tests for which the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care). See *Appendix 12* for more detail.

Additional sensitivity analyses

Appendix 13, *Table 64*, displays the list of the 39 deterministic sensitivity analyses conducted to explore the impact of alternative modelling assumptions and parameter inputs on base-case ICERs. In the majority of cases, the ICERs were robust to the implemented changes in the majority of the analyses implemented, and the base-case cost-effectiveness conclusions remain unchanged. In particular, assuming a shorter 14-day time horizon (sensitivity analysis 3) that is consistent with the typical duration and resolution of symptoms of strep A sore throat infection favoured usual care but the ICERs did not change substantially to suggest a different interpretation of the base-case cost-effectiveness. Assuming that the treating primary care health-care professional in both the intervention arm and the usual-care arm is a nurse or a pharmacist (sensitivity analysis 19) rather than a GP favoured testing, only if the test cannot be carried out within the allocated consultation time. In this instance, the costs associated with the additional clinician time taken to administer and process test results are much lower if seen by a nurse or pharmacist than if the treating clinician is a GP. Similarly, excluding the cost of the additional clinician time required to process test results (sensitivity analysis 22) favoured testing only where testing cannot be done within allocated primary care consultation time.

Summary of economic modelling

We undertook a systematic search for economic evaluation studies of the use of point-of-care tests as listed in the NICE scope for patients with suspected strep A infection. We did not identify any relevant economic models that could be adapted. Hence, a de novo decision tree model was built to compare point-of-care testing in conjunction with clinical scoring tools with clinical scoring tools alone for children and adults presenting with strep A infection in primary and secondary care settings.

The model took account of the presenting prevalence of disease in the modelled population, accuracy of clinical scoring and testing, the prescribing behaviour of treating clinicians and complications of the infection and treatment. In the base-case analysis, costs were calculated from a UK NHS/Personal Social Services perspective over the 1-year time horizon. The health impact of intervention was expressed in QALYs captured through application of disutilities associated with treated and untreated infection and related complications over the modelled time horizon.

The scope of the appraisal had called for 21 tests to be evaluated in comparison with usual-care practice; however, difficulties in obtaining reliable test accuracy and cost data for all tests meant that we were able to include only 14 of the 21 tests for which relevant data were available in final economic modelling. Under the base-case model assumptions for adults presenting with suspected strep A in primary care, the ICER suggests that usual care dominated two tests (Clearview Exact Strep A cassette and Clearview Exact Strep A dipstick – test strip, both supplied by Abbott Laboratories). For the remaining 12 tests, testing was marginally more effective and more costly than usual care, with ICERs ranging from £1,353,677 per QALY gained for NADAL Strep A test strip (nal von minden GmbH) to £6,059,081 per QALY for Roche Diagnostics' cobas Liat Strep A Assay compared with usual care.

Probabilistic analyses based on 1000 Monte Carlo simulations of the ICER assessed parameter uncertainty and generated probability statements about the cost-effectiveness of point-of-care testing across a range of willingness-to-pay thresholds. Probabilistic ICERs produced results similar to the deterministic base-case

ICERs, and suggested that testing was associated with zero probability of cost-effectiveness at willingness-to-pay thresholds of £0 to £100,000 per QALY gained under base-case assumptions. Similar cost-effectiveness results were obtained in the base-case models for adults presenting in secondary care, and in primary and secondary care models for children.

Extensive exploratory deterministic sensitivity analyses of the base-case inputs and assumptions were conducted to understand key model drivers. The findings suggest that the ICER is highly sensitive to (1) parameter inputs and assumptions that increase the cost of testing (acquisition cost of test, additional clinician time for administering and processing test results, and cost of confirmatory throat culture for those testing negative) and (2) the penalty for antibiotic overprescription/unnecessary antibiotic use (acquisition cost of antibiotic and probabilities for penicillin-induced anaphylaxis and rash). Factoring in costs associated with additional clinician time (at £4 per minute of GP time) for administering tests and £8 for a confirmatory throat culture given a negative test in the base case both favour usual care, as these costs can be substantially higher than the actual cost of the test and are applied to the intervention arm only. In contrast, the model predicts lower antibiotic use with testing than with usual care; however, the cost of antibiotic treatment, at £0.91 per course of penicillin, the treatment of choice for strep A infection, is considerably cheaper (than the acquisition costs for the majority of the test kits), such that the penalty for supplying antibiotics to those who do not need it is negligible compared with the cost of testing.

The base case incorporates serious adverse effects of penicillin, such as penicillin-induced anaphylaxis, with associated high treatment costs and disutility; however, the modelled rate of 0.01%[78] used in the base case suggests that anaphylaxis is very rare and its impact is, therefore, minimal on the cost-effectiveness of testing. Sensitivity analyses increasing the rate of anaphylaxis to 0.64% based on another economic evaluation of strep A pharyngitis[79] favoured testing: the ICER for Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A cassette (Abbott Laboratories) changed from being dominated by usual care in the base case to £288,702 and £299,305 per QALY gained compared with usual care, respectively.

Cost-effectiveness estimates were also sensitive to the prevalence of strep A infection (higher prevalence favouring usual care and lower prevalence favouring testing), the disutility for untreated infection (lower values favoured testing and doubling the decrement associated with untreated infection favoured usual care) and the disutility for treated strep A infection (doubling the disutility favours testing).

Points for discussion regarding the economic modelling

A number of limitations apply to the economic model:

- Although the economic model represented the clinical care pathway in the NHS, practice and management will vary from site to site (within and across primary and secondary care settings).
- The majority of inputs for test performance came from data on populations that were not directly relevant to the location of the tests in our modelled health-care pathway (e.g. were not specific to patients with Centor scores of ≥ 3 points). Hence, the true performance of the tests could differ from the current models.
- We could compare point-of-care testing for only 14 of the 21 tests listed in the NICE scope, as we did not have test accuracy and/or cost data for the other seven point-of-care tests.
- There was not enough information on test accuracy data to model strep A infection in the pharmacy setting or for the elderly population.
- Inputs (except for the sensitivity and specificity data from our effectiveness review) were generally available as point estimates without associated measures of uncertainty, such as CIs and SEs, required for probabilistic modelling. Thus, we have had to follow the common practice of assuming $\pm$ 10% around the central estimate to incorporate uncertainty in our modelling. This approach to probabilistic analysis is itself associated with degree of uncertainty, as it may underestimate or overestimate the true uncertainty in the evidence.

- Our protocol had specified a time horizon of 14 days, as the evidence suggests that strep A infection is a self-limiting illness with the majority of patients making a complete recovery within 2 weeks of the infection.[86] However, we extended the time horizon to 1 year in the base-case model to accommodate the impact of rare complications of strep A, such as acute rheumatic fever, where we found evidence to suggest that these complications could be associated with as many as 75 quality-adjusted life-days lost.[78–80] However, this longer time horizon required further assumptions to keep the modelling feasible and supported by appropriate evidence. In particular, we assumed only one episode of strep A infection (the initial index episode) per patient with no possibility of a recurrent infection within the 1-year time horizon, which is unlikely to represent a true reflection of sore throat infections in the community (these point-of-care tests would not be used in people with recurrent sore throats and this was excluded from the scope of work). Extending the time horizon to 1 year may also not adequately capture all costs and consequences associated with infection. For example, there is evidence suggesting that increased risk of death from rheumatic heart disease is associated with complications of strep A,[82,83] but this cannot be fully incorporated within the 1-year time horizon considered in our base case.
- We did not explore the impact of a lifetime horizon on the cost-effectiveness point-of-care testing because (1) strep A infection is a self-limiting illness (see point above) and (2) the decision tree structure is not suitable for economic models with lifetime modelling. The model does, however, account for rare but serious complications of the infection, such as acute rheumatic fever and anaphylactic reactions to penicillin, both of which can have a long-lasting impact. For these, we assume that the 1-year time horizon considered in the base case is sufficient to capture the costs and consequences associated with such complications.
- Sensitivity analyses assuming a shorter time horizon of 2 weeks (14 days), corresponding to the expected time for symptom resolution, did not alter the conclusions of the base-case cost-effectiveness results.
- Although the model captures the unwanted effects of antibiotic treatment, such as penicillin-induced rash and anaphylaxis, through incorporating appropriate costs and disutility for these events, resistance to antimicrobial therapy was not explicitly modelled because of evidence suggesting that strep A is highly susceptible to penicillin[83,94] (the treatment of choice for strep A infection).
- The model captures suppurative and non-suppurative complications of strep A infection and the unwanted effects of penicillin use. The probability estimates for suppurative complications were derived from combining data for all such complications (quinsy, sinusitis, otitis media and cellulitis) reported in a large UK cohort study by Little *et al.*[86] As the Little *et al.*[86] data include figures for non-suppurative complications of the infection, such as the acute rheumatic fever, all such complications were included in the modelling under the assumption that majority of complications of strep A infection were suppurative, with no more than 0.01% being non-suppurative. Sensitivity analysis suggests that this assumption has minimal impact on the base-case cost-effectiveness results. Other complications of the strep A infection not included in the economic modelling include mortality outcomes and scarlet fever in the children's models because of a lack of data informing probability estimates for these events; hence, the costs may be underestimated and outcomes overestimated in the models.
- Transmissions between infected and susceptible individuals are not modelled because of a lack of evidence to inform transmission rates in dynamic disease modelling. There is also evidence to suggest seasonality effect (e.g. an increased presentation of strep A infection during the winter months and around Easter time), but this was not explicitly modelled. However, we carried out exploratory analysis in which we varied the prevalence of disease, which can be taken as proxy for seasonality effect. These exploratory analyses suggest that increasing prevalence of disease among adults and children in primary care generally favoured usual care, but the ICERs did not change substantially to suggest a different conclusion from the base-case cost-effectiveness results. In contrast, lowering the prevalence favoured testing, but, again, the ICERs did not change substantially to alter conclusions of the base-case analyses.

- The modelling may have underestimated the costs as we did not take into account the contribution to antimicrobial stewardship owing to the lack of evidence.
- The model has not accounted for certain high-risk populations, such as immunosuppressed patients or pregnant women, as these patients would all be offered antibiotics.
- We have not taken into account that some of these point-of-care tests may also detect other strains of strep infections, such as strep C and strep G, in addition to strep A.
- The modelling may have underestimated the costs as we did not take into account the different strains of strep A that may have influenced test performance and disease characteristics, potentially altering the profile of complications.
- We did not consider the impact that introducing routine point-of-care testing might have on patient presentation with sore throat, which could influence the cost-effectiveness results.
- We did not place any monetary value on the impact a point-of-care test might have in including the patient in the treatment decision-making process.
- We have not taken into account any broader societal costs, such as lost productivity or time off work, owing to suspected strep A infection.
- Finally, modelled changes in costs and QALYs are simulations and have not been observed. Findings should be verified through properly designed and conducted research.

Chapter 5 Discussion

Decision problem and objectives

The overall objective was to undertake a clinical effectiveness and cost-effectiveness analysis of rapid antigen detection and molecular tests in those with high clinical scores, compared with the use of clinical scoring tools alone, for increasing the diagnostic confidence of suspected group A streptococcal infection in people who present with an acute sore throat in primary and secondary care settings. The literature informing clinical effectiveness and cost-effectiveness was systematically reviewed and summarised. A de novo economic model was developed to assess the cost-effectiveness of rapid antigen detection and molecular tests in conjunction with clinical scoring tools compared with clinical scoring tools alone in England and Wales.

Summary of methods and findings

Clinical effectiveness

We searched a number of databases including MEDLINE, EMBASE, Web of Science and The Cochrane Library. We found 3309 unique records, of which 38 were included [26 full-text articles, three abstracts, five manufacturers' submissions (submitted to NICE in response to a request for information) and four FDA documents]. There were 26 studies that reported on test accuracy data. In general, the methodological quality of the included studies was poor. In particular, in 65.4% (17/26) of studies it was unclear whether the sample was consecutive or convenience. Convenience samples may not provide a true representation of the prevalence of strep A. There was judged to be a high level of bias surrounding the subjective reading of some of the point-of-care tests and through lack of adherence to manufacturer's guidance by using the same swab to streak the microbiological culture and then conduct the point-of-care test. In addition, microbiological culture is unlikely to be 100% accurate and may vary with different culture media.

Overall, the findings reveal wide variations in the point estimates for the sensitivity (67.9% to 100%) and specificity (73.3% to 100%) of the different point-of-care tests. These estimates were 82.9% to 94.6% for sensitivity and 84.9% to 99.1% for specificity in high-risk populations, including patients with Centor/McIsaac scores of > 2 points, representing the population of interest. These estimates do not account for any of the unpublished manufacturer submissions.

Clinical scoring tools (FeverPAIN and Centor) have been proposed as a method by which clinicians can identify which patients are most likely to benefit from antibiotic use for sore throat.[8] These tools were developed to predict strep A (Centor and FeverPAIN), strep C (FeverPAIN) and strep G (FeverPAIN). Direct comparison between sore throat clinical scoring tools and point-of-care tests indicated that specificity estimates were higher for the point-of-care tests, and that sensitivity was generally comparable between the two approaches. Direct comparison with sore throat clinical scoring tools revealed that point-of-care tests were generally more specific. However, one methodological limitation concerns the varying way that clinical scoring tools have been implemented across the included studies. For instance, different studies apply different clinical cut-off points when recruiting patients. No studies were identified that matched the proposed pathway of care and treatment for patients with acute streptococcal pharyngitis, which would entail evaluating the test accuracy of a combined strategy of sore throat clinical scores at the recommended NICE thresholds (Centor/McIsaac score of ≥ 3 points or FeverPAIN score of ≥ 4 points) and point-of-care tests. No evidence was identified for the elderly population or in a pharmacy setting. Likewise, data for test accuracy were sparse for each combination of test, population and setting. There were very few head-to-head (direct) comparison studies between index tests.

It was not possible to identify which test is the most accurate owing to the lack of evidence. The large degree of heterogeneity among results for studies using the same rapid test suggests that it is unlikely that any single study will accurately capture a test's true performance. The apparent accuracy of a test may be penalised for having more studies, compared with tests with a single study, particularly those in which the manufacturer has conducted that study. The heterogeneity introduced by the differing characteristics of the studies further confounded attempts to produce meaningful estimates of test performance, such as care setting, age group, throat score restriction and disease prevalence. Owing to the potential heterogeneity, estimates for the sensitivity and specificity of each test were stratified by age group, throat score and care setting, although a lack of evidence meant that generalisations had to be made for the majority of estimates.

There is some RCT evidence to suggest that the use of RADTs may help to reduce antibiotic-prescribing rates, but there was no evidence on the effect of using molecular technologies. If a test was proven to be extremely accurate, then it is plausible that clinical staff would trust the outcomes. No evidence was found on time to antimicrobial prescribing decision, number of appointments required per episode and onward transmission of infection.

Cost-effectiveness

The systematic review of cost-effectiveness studies identified three studies that used the RADTs as identified in the NICE scope and were classed as economic evaluations. Two studies had some notable limitations and could not be fully data extracted. The one study that allowed a full data extraction was classed as a high-quality economic evaluation when checked against the CHEERS reporting tool.

Fourteen of the 21 tests listed in the NICE scope had data on test accuracy and costs relevant to be included in the final economic modelling. In the base-case analysis, which included adult patients seen in primary care with suspected strep A infection, the economic model found point-of-care testing to not be cost-effective compared with usual care for suspected strep A infection. This finding was also seen in the other economic models, which were adapted for the different patient groups and settings (adult patients seen in the hospital, children seen in primary care and children seen in the hospital). Important uncertainties in the model include parameter inputs and assumptions that increase (1) the cost of testing (acquisition cost of test, additional clinician time for administering and processing test results, and cost of confirmatory throat culture for those testing negative) and (2) the penalty for antibiotic overprescription/unnecessary antibiotic use (acquisition cost of antibiotic and probabilities for penicillin-induced anaphylaxis and rash).

Strengths and limitations

We used a rigorous and exhaustive search to conduct a comprehensive systematic review (literature search, data extraction and analysis) and locate primary studies. All relevant studies were systematically reviewed and agreement between the two reviewers was very high. We also built a de novo decision tree model to assess cost-effectiveness of point-of-care testing. The economic model provides a representation of the clinical care pathway in primary and secondary care settings. The decision tree was populated with probabilities and test accuracy values from the clinical evidence review, published studies and clinical expert opinion.

No studies of point-of-care test use in a pharmacy setting or in the elderly population were retrieved. In addition, no study matched the proposed pathway of care and treatment for patients with acute streptococcal pharyngitis, which would entail evaluating the test accuracy of a combined strategy of sore throat clinical scores at the recommended NICE thresholds (Centor/McIsaac score of ≥ 3 points or FeverPAIN score of ≥ 4 points) and point-of-care tests in the age groups defined in the scope.

Children aged < 5 years were not explicitly considered in this review. Although they may benefit from a point-of-care test, following advice from health-care professionals, we understood that their diagnostic pathway is likely to differ from older age groups, and they were considered beyond the scope of this review.

For the purpose of this review, we classified GP surgeries, health-care centres, family practices and primary care clinics as primary care. Secondary care comprised emergency departments, private paediatric clinics, outpatient clinics, urgent care clinics and walk-in centres. In practice, other countries may define primary and secondary care differently; for example, paediatric clinics could be part of primary care. However, given that it is unclear if test accuracy differs by setting, we do not know the impact this could have on the cost-effectiveness estimates.

We included only English-language studies and studies directly matching the test name, unless we had confirmation that a test had been taken over by another manufacturer (e.g. in the case of IMI testpack becoming Alere). We did not include studies where it was unclear whether or not later iterations of the test were different. During the EAG write-up of the final report, Abbott Laboratories notified NICE that the Alere i Strep A test was no longer available. The Alere i Strep A 2 has been rebranded as the ID NOW Strep A 2. Our previously excluded studies were rescreened by test name, and none used the ID NOW Strep A 2 test. It is the EAG's understanding that the information in this report relevant to the Alere i Strep A 2 is transferable to the ID NOW Strep A 2. In addition, the Clearview Exact Strep A tests (both cassette and dipstick) were replaced with new Clearview Exact Strep A 2 editions. The manufacturers supplied NICE with information that there are procedural differences between previous Clearview tests and the new A 2 editions. Therefore, the results for the Clearview Exact Strep A tests in this review may not be generalisable to the current Clearview products on the market. Furthermore, our previously excluded studies were rescreened by test name, and none used the Clearview Exact Strep A 2 editions.

We did not explore the effect of culture medium on test accuracy in the review. One of the included test accuracy studies found that using different culture media was showing strep A positivity on samples that were initially negative.[42] This could indicate possible differences in accuracy of different culture media.

Test accuracy may also vary greatly based on the quality of the swabbing. It is unclear how the level of training of clinical staff involved in these studies compares with routine care, which could limit the generalisability of these results.

The evidence informing the test accuracy estimates was not sufficient to produce reliable or robust estimates that we could be confident actually reflected the tests' true performance in any particular patient group. The main concern is that the patients' clinical scores used in the studies of test accuracy did not match the scores of patients anticipated to benefit from using the tests, as modelled in our economic analysis. The health-care setting and age group were also potential variables that may affect test performance. This concern extends to the economic modelling, which used the estimates for each test.

The studies in this review determined antibiotic appropriateness to be based on strep A positivity in the culture. However, culture may detect strep A carriage as opposed to disease. PCR was a potential alternative reference standard, but was less widely used, and encounters the same issue of carriage detection.

Although the economic model represented the clinical care pathway in the NHS, practice and management will vary from site to site (within and across both primary care and secondary care settings). There was not enough information on test accuracy data to model strep A for the pharmacy setting or for the elderly population. Furthermore, we could compare only 14 of the 21 point-of-care tests as listed in the NICE scope, as we did not have test accuracy and/or cost data for the other seven point-of-care tests. The modelling may have underestimated the costs as we did not take into account the different strains of strep A that may have influenced test performance and altered the profile of complications, seasonality of strep A infection, resistance to antimicrobial therapy, the onward transmission of the infection and the broader societal costs.

Chapter 6 Conclusions

The systematic review and cost-effectiveness model identify uncertainties around the adoption of point-of-care tests in primary and secondary care settings in England and Wales. The available evidence is heterogeneous in populations studied, design, methods and analysis. Although sensitivity and specificity estimates are promising, we have little information on the best point-of-care test to use. Although there is potential for the point-of-care tests to be cost-effectiveness in both primary care and secondary care settings, key parameter inputs and modelling assumptions need to be confirmed and model findings remain uncertain.

Recommendations for future research

Further research is needed to understand the test accuracy of point-of-care tests in the proposed NHS pathway and in comparable settings and patient groups. There was a considerable lack of evidence for the performance of the tests based on real-world use in patients with a Centor score of ≥ 3 points or a FeverPAIN score of ≥ 4 points. Future work that considers head-to-head test accuracy studies or RCTs using multiple point-of-care tests in relevant patient populations and health-care settings considered in the NICE scope would provide relevant comparator information and help to determine the value of point-of-care testing. Results broken down by relevant subgroups, such as age and clinical score threshold, would also be useful. Further research on the establishment of a gold reference standard with which tests are compared would also reduce uncertainty and potential bias in reviews such as this.

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All authors were involved in writing draft and final versions of the report.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Please note that exclusive use will be retained until the publication of major outputs.

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Appendix 1 Record of searches: clinical effectiveness

Bibliographic databases

Summary of bibliographic database searches

Database	Date of search	Number of records (+ number from update search)
MEDLINE (via OvidSP)	26 November 2018 (updated 7 March 2019)	1646 (+ 33)
EMBASE (via OvidSP)	27 November 2018 (updated 12 March 2019)	2546 (+ 177)
The Cochrane Library (via Wiley Online Library)	29 November 2018 (updated 12 March 2019)	118 (+ 1)
Science Citation Index and Conference Proceedings Citation Index – Science (via the Web of Science)	3 December 2018 (updated 12 March 2019)	1275 (+ 67)
DARE (via CRD)	22 January 2019 (updated 12 March 2019)	30 (+ 0)
HTA (via CRD)	22 January 2019 (updated 12 March 2019)	2 (+ 0)

Total number of records from database searches: 5617 (+ 278 from 2019 update search) = 5895.
Total number of records after deduplication: 3240 (+ 45 from 2019 update search) = 3285.

MEDLINE (via OvidSP)

Databases: Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions.

Date searched: 26 November 2018 (updated on 7 March 2019; see the end of this search record).

Date range searched: 1946 to 21 November 2018.

Original search: 26 November 2018

Search strategy

1. exp Pharyngitis/ (15,049)
2. pharyngit*.ti,ab,kf. (5455)
3. (nasophyryngit* or rhinopharyngit* or epipharyngit*).ti,ab,kf. (177)
4. (tonsillit* or tonsilit*).ti,ab,kf. (5589)
5. ((sore or pain* or ache* or aching or inflam* or infect*) adj3 (pharyn* or throat* or tonsil* or nasopharyn* or rhinopharyn* or epipharyn*)).ti,ab,kf. (9903)
6. or/1-5 (25,137)
7. Streptococcal Infections/di, mi (13,347)
8. Streptococcus pyogenes/im, ip (5444)
9. 7 or 8 (16,609)
10. ((strep or streptococcal or group) adj2 A).ti,ab,kf. (558,959)
11. 9 and 10 (4831)

12. (strep* adj5 (throat* or pharyn* or tonsil*)).ti,ab,kf. (3397)
13. streptoco* A.ti,ab,kf. (475)
14. (group A adj5 streptoco*).ti,ab,kf. (9481)
15. ((streptococcus or strep) adj1 (pyogenes or pyogenic)).ti,ab,kf. (7683)
16. ((streptococcus or strep) adj1 (epidemicus or erysipelatis or erysipelatos or hemolyticus or haemolyticus or scarlatinae or lancefield)).ti,ab,kf. (237)
17. (s pyogenes or pyogenes s or micrococcus scarlatinae).ti,ab,kf. (2485)
18. lancefield group.ti,ab,kf. (475)
19. gabhs.ti,ab,kf. (392)
20. or/11-19 (18,796)
21. Point-of-Care Systems/ (11,122)
22. exp Reagent Kits, Diagnostic/ (19,326)
23. Antigens, Bacterial/an (7619)
24. (point-of-care or poc or poct or pocts).ti,ab,kf. (17,665)
25. ((rapid* or bedside*1 or bed-side*1 or near-patient or nearpatient or extra-laboratory or extralaboratory or office*1) adj6 (test or tests or testing or tested or detect* or diagnos* or screen* or kit or kits or assay* or immunoassay* or determin* or identif* or antigen*1)).ti,ab,kf. (136,637)
26. (radt or radts or rdt or rdts).ti,ab,kf. (1813)
27. (antigen*1 adj6 (test or tests or testing or tested or detect* or diagnos* or screen* or kit or kits or assay* or immunoassay* or determin* or identif*)).ti,ab,kf. (100,724)
28. (clearview exact* or BD veritor* or strep A rapid test* or quikread go* or alere i* or cobas liat* or genexpert* or ((alere* or testpack* or test-pack* or bionexia* or bio-nexia* or biosynex* or veritor* or cobas* or quikread* or quik-read* or NADAL* or OSOM* or sofia* or xpert*) and (strep A or point of care or point-of-care or POC))).ti,ab,kf. (804)
29. ((abbott or beckton dickinson or biopanda or nal von minden or sekisui or orion diagnostica or roche or cepheid or biomerieux or quidel) and (strep A or point of care or POC or rapid test* or rapid antigen or antigen test*)).ti,ab,kf,in. (618)
30. or/21-29 (269,698)
31. (6 or 20) and 30 (1759)
32. exp animals/ not humans/ (4,517,568)
33. 31 not 32 (1646)
34. 31 use medp,prem,mesx (114)
35. 33 or 34 (1646).

Updated search: 7 March 2019

Search strategy

Re-ran above search with the following date limits:

36. limit 35 to ed=20181126-20190307 (17)
37. limit 35 to ep=20181126-20190307 (14)
38. (2018 11* or 2018 12* or 2019*).dt,ez. (243,915)
39. 35 and 38 (13)
40. 36 or 37 or 39 (33)

Total after removing duplicates with previous search: 16.

EMBASE (via OvidSP)

Databases: EMBASE Classic and EMBASE.

Date searched: 27 November 2018 (updated on 12 March 2019; see the end of this search record).

Date range searched: 1947 to 21 November 2018.

Original search: 27 November 2018

Search strategy

1. streptococcal pharyngitis/ or pharyngitis/ or rhinopharyngitis/ or sore throat/ or tonsillitis/ or chronic tonsillitis/ or palatine tonsillitis/ (51,206)
2. pharyngit*.ti,ab,kw. (7851)
3. (nasophyryngit* or rhinopharyngit* or epipharyngit*).ti,ab,kw. (379)
4. (tonsillit* or tonsilit*).ti,ab,kw. (8320)
5. ((sore or pain* or ache* or aching or inflam* or infect*) adj3 (pharyn* or throat* or tonsil* or nasopharyn* or rhinopharyn* or epipharyn*)).ti,ab,kw. (15,900)
6. or/1-5 (59,836)
7. Streptococcus infection/di (3821)
8. Streptococcus pyogenes/ or streptococcus group a/ or group A streptococcal infection/ (23,921)
9. 7 or 8 (26,865)
10. ((strep or streptococcal or group) adj2 A).ti,ab,kw. (792,961)
11. 9 and 10 (9617)
12. (strep* adj5 (throat* or pharyn* or tonsil*)).ti,ab,kw. (4842)
13. streptoco* A.ti,ab,kw. (636)
14. (group A adj5 streptoco*).ti,ab,kw. (12,213)
15. ((streptococcus or strep) adj1 (pyogenes or pyogenic)).ti,ab,kw. (9259)
16. ((streptococcus or strep) adj1 (epidemicus or erysipelatis or erysipelatos or hemolyticus or haemolyticus or scarlatinae or lancefield)).ti,ab,kw. (388)
17. (s pyogenes or pyogenes s or micrococcus scarlatinae).ti,ab,kw. (3223)
18. lancefield group.ti,ab,kw. (567)
19. gabhs.ti,ab,kw. (504)
20. or/11-19 (24,055)
21. point of care system/ or point of care testing/ (11,966)
22. rapid test/ or diagnostic kit/ (8892)
23. antigen detection/ or bacterial antigen/an or Streptococcus antigen/ (24,501)
24. (point-of-care or poc or poct or pocts).ti,ab,kw. (25,553)
25. ((rapid* or bedside*1 or bed-side*1 or near-patient or nearpatient or extra-laboratory or extralaboratory or office*1) adj6 (test or tests or testing or tested or detect* or diagnos* or screen* or kit or kits or assay* or immunoassay* or determin* or identif* or antigen*1)).ti,ab,kw. (177,813)
26. (radt or radts or rdt or rdts).ti,ab,kw. (2974)
27. (antigen*1 adj6 (test or tests or testing or tested or detect* or diagnos* or screen* or kit or kits or assay* or immunoassay* or determin* or identif*)).ti,ab,kw. (130,835)
28. (clearview exact* or BD veritor* or strep A rapid test* or quikread go* or alere i* or cobas liat* or genexpert* or ((alere* or testpack* or test-pack* or bionexia* or bio-nexia* or biosynex* or veritor* or cobas* or quikread* or quik-read* or NADAL* or OSOM* or sofia* or xpert*) and (strep A or point of care or point-of-care or POC))).ti,ab,kw. (1633)
29. ((abbott or beckton dickinson or biopanda or nal von minden or sekisui or orion diagnostica or roche or cepheid or biomerieux or quidel) and (strep A or point of care or POC or rapid test* or rapid antigen or antigen test*)).ti,ab,kw,in. (1404)
30. or/21-29 (345,022)
31. (6 or 20) and 30 (2856)
32. (exp animal/ or nonhuman/) not exp human/ (6,749,742)
33. 31 not 32 (2546)

Updated search: 12 March 2019

Search strategy

Re-ran above search with the following date limits:

34. limit 33 to dd=20181127-20190312 (18)
35. limit 33 to em=201811-201903 (152)
36. 34 or 35 (159)
37. limit 33 to dc=20181127-20190312 (41)
38. 36 or 37 (177)

Total after removing duplicates with other update and previous searches: 25.

The Cochrane Library (including Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials)

Date searched: 29 November 2018 (updated on 12 March 2019; see the end of this search record).

Original search: 29 November 2018

Search strategy

#1 MeSH descriptor: [Pharyngitis] explode all trees (1138)
#2 pharyngit*:ti,ab,kw (1916)
#3 (nasophyryngit* or rhinopharyngit* or epipharyngit*):ti,ab,kw (2597)
#4 (tonsillit* or tonsilit*):ti,ab,kw (826)
#5 ((sore or pain* or ache* or aching or inflam* or infect*) near/3 (pharyn* or throat* or tonsil* or nasopharyn* or rhinopharyn* or epipharyn*)):ti,ab,kw (3198)
#6 #1 or #2 or #3 or #4 or #5 (7030)
#7 MeSH descriptor: [Streptococcal Infections] explode all trees and with qualifier(s): [diagnosis - DI, microbiology - MI] (306)
#8 MeSH descriptor: [Streptococcus pyogenes] explode all trees and with qualifier(s): [immunology - IM, isolation & purification - IP] (89)
#9 #7 or #8 (351)
#10 ((strep or streptococcal or group) near/2 A):ti,ab,kw (109,570)
#11 #9 and #10 (126)
#12 (strep* near/5 (throat* or pharyn* or tonsil*)):ti,ab,kw (499)
#13 streptoco* next A:ti,ab,kw (26)
#14 (group A near/5 streptoco*):ti,ab,kw (689)
#15 ((streptococcus or strep) near/1 (pyogenes or pyogenic)):ti,ab,kw (423)
#16 ((streptococcus or strep) near/1 (epidemicus or erysipelatis or erysipelatos or hemolyticus or haemolyticus or scarlatinae or lancefield)):ti,ab,kw (1)
#17 ("s pyogenes" or "pyogenes s" or "micrococcus scarlatinae"):ti,ab,kw (60)
#18 "lancefield group":ti,ab,kw (6)
#19 gabhs:ti,ab,kw (109)
#20 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 (1123)
#21 MeSH descriptor: [Point-of-Care Systems] explode all trees (424)
#22 MeSH descriptor: [Reagent Kits, Diagnostic] explode all trees (267)
#23 MeSH descriptor: [Antigens, Bacterial] explode all trees and with qualifier(s): [analysis - AN] (63)
#24 (point-of-care or poc or poct or pocts):ti,ab,kw (2560)
#25 ((rapid* or bedside*1 or bed-side*1 or near-patient or nearpatient or extra-laboratory or extralaboratory or office*1) near/6 (test or tests or testing or tested or detect* or diagnos* or screen* or kit or kits or assay* or immunoassay* or determin* or identif* or antigen*1)):ti,ab,kw (3506)
#26 (radt or radts or rdt or rdts):ti,ab,kw (302)

#27 (antigen*1 near/6 (test or tests or testing or tested or detect* or diagnos* or screen* or kit or kits or assay* or immunoassay* or determin* or identif*)):ti,ab,kw (0)
#28 (clearview next exact* or BD next veritor* or "strep A rapid" next test* or quikread next go* or alere next i* or cobas next liat* or genexpert* or ((alere* or testpack* or test-pack* or bionexia* or bio-nexia* or biosynex* or veritor* or cobas* or quikread* or quik-read* or NADAL* or OSOM* or sofia* or xpert*) and ("strep A" or "point of care" or point-of-care or POC))):ti,ab,kw (114)
#29 ((abbott or "beckton dickinson" or biopanda or "nal von minden" or sekisui or "orion diagnostica" or roche or cepheid or biomerieux or quidel) and ("strep A" or "point of care" or POC or rapid next test* or rapid next antigen* or antigen next test*)):ti,ab,kw (47)
#30 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 (6235)
#31 (#6 or #20) and #30 (118)

Total: 118.

- Cochrane Database of Systematic Reviews – Reviews: 15.
- Cochrane Database of Systematic Reviews – Protocols: 1.
- CENTRAL: 102.

Updated search: 12 March 2019
Re-ran above search and sorted by date, with the newest first.

New since 29 November 2018:

- Cochrane Database of Systematic Reviews – Reviews: 0
- Cochrane Database of Systematic Reviews – Protocols: 0
- CENTRAL: 1.

Total after removing duplicates with other update and previous searches: 0.

Science Citation Index and Conference Proceedings (via the Web of Science)
Date searched: 3 December 2018 (updated on 12 March 2019; see the end of this search record).

Original search: 3 December 2018
Note: search record reads from bottom to top.

Search strategy
Note: search record reads from bottom to top.

Set	Results	History
# 23	1275	(#5 OR #14) AND #22 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 22	265,727	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*
# 21	487	TS=((abbott OR "beckton dickinson" OR biopanda OR "nal von minden" OR sekisui OR "orion diagnostica" OR roche OR cepheid OR biomerieux OR quidel) AND ("strep A" OR "point* of care" OR poc OR poct OR pocts OR "rapid test*" OR "rapid antigen" OR "antigen test*")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=All years*

Set	Results	History
# 20	849	TS=("clearview exact*" OR "BD veritor*" OR "strep A rapid test*" OR "quikread go*" OR "alere i*" OR "cobas liat*" OR genexpert* OR ((alere* OR testpack* OR test-pack* OR bionexia* OR bio-nexia* OR biosynex* OR veritor* OR cobas* OR quikread* OR quik-read* OR NADAL* OR OSOM* OR sofia* OR xpert*) AND ("strep A" OR "point* of care" OR poc OR poct OR pocts)))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 19	86,024	TS=(antigen* NEAR/5 (test OR tests OR testing OR tested OR detect* OR diagnos* OR screen* OR kit OR kits OR assay* OR immunoassay* OR determin* OR identif*))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 18	2261	TS=(radt OR radts OR rdt OR rdts)
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 17	165,166	TS=((rapid* OR bedside* OR bed-side* OR near-patient OR nearpatient OR extra-laboratory OR extralaboratory OR office*) NEAR/5 (test OR tests OR testing OR tested OR detect* OR diagnos* OR screen* OR kit OR kits OR assay* OR immunoassay* OR determin* OR identif* OR antigen*))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 16	22,883	TS=("point* of care" OR poc OR poct OR pocts)
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 15	219	TS=(diagnostic AND (reagent NEAR/0 (kit* OR strip*)))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 14	17,280	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 13	308	TS=gabhs
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 12	444	TS="lancefield group"
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 11	2042	TS=("s pyogenes" OR "pyogenes s" OR "micrococcus scarlatinae")
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 10	59	TS=((strep*) NEAR/0 (epidemicus OR erysipelatis OR erysipelatos OR hemolyticus OR haemolyticus OR scarlatinae OR lancefield))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 9	7107	TS=((strep*) NEAR/0 (pyogenes OR pyogenic))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 8	9638	TS=("group A" NEAR/4 strep*)
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 7	1156	TS="strep* A"
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 6	2875	TS=(strep* NEAR/4 (throat* OR pharyn* OR tonsil*))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 5	12,426	#1 OR #2 OR #3 OR #4
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

Set	Results	History
# 4	6980	TS=((sore OR pain* OR ache* OR aching OR inflam* OR infect*) NEAR/2 (pharyn* OR throat* OR tonsil* OR nasopharyn* OR rhinopharyn* OR epipharyn*))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 3	2703	TS=(tonsillit* OR tonsilit*)
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 2	96	TS=(nasophyryngit* OR rhinopharyngit* OR epipharyngit*)
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 1	4651	TS=pharyngit*
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

Updated search: 12 March 2019

Re-ran the above search with the following date limits:

Search strategy

# 23	67	(#5 OR #14) AND #22
		Indexes=SCI-EXPANDED, CPCI-S Timespan=2018-2019

Total after removing duplicates with other update and previous searches: 4.

Database of Abstracts of Reviews of Effects (via Centre for Reviews and Dissemination) and Health Technology Assessment database (via Centre for Reviews and Dissemination)

Date searched: 22 January 2019. (Not updated because no new records have been added to DARE since 31 March 2015 or to the HTA database since 31 March 2018. The INAHTA website was checked in March 2019 to see if a new platform for the HTA database was available.)

Original search: 22 January 2019

Search strategy

1. MeSH DESCRIPTOR Pharyngitis EXPLODE ALL TREES IN DARE,NHSEED,HTA (73)
2. (pharyngit*) (85)
3. (nasophyryngit*) OR (rhinopharyngit*) OR (epipharyngit*) (5)
4. (tonsillit* or tonsilit*) (43)
5. (((sore or pain* or ache* or aching or inflam* or infect*) adj3 (pharyn* or throat* or tonsil* or nasopharyn* or rhinopharyn* or epipharyn*))) (91)
6. #1 OR #2 OR #3 OR #4 OR #5 (163)
7. MeSH DESCRIPTOR Streptococcal Infections WITH QUALIFIERS DI, MI IN DARE, NHSEED,HTA (31)
8. MeSH DESCRIPTOR Streptococcus pyogenes WITH QUALIFIERS IM, IP IN DARE, NHSEED,HTA (13)
9. #7 OR #8 (36)
10. ((strep or streptococcal or group) adj2 A)) (2025)
11. #9 AND #10 (17)
12. ((strep* adj5 (throat* or pharyn* or tonsil*))) (39)
13. (streptoco* adj1 A) (10)
14. ((group A adj5 streptoco*)) (27)

15. (((streptococcus or strep or staphylococcus) adj1 (pyogenes or pyogenic))) (25)
16. (((streptococcus or strep) adj1 (epidemicus or erysipelatis or erysipelatos or hemolyticus or haemolyticus or scarlatinae or lancefield))) (0)
17. ((s pyogenes or pyogenes s or micrococcus scarlatinae)) (1)
18. (lancefield group) (0)
19. (gabhs) (8)
20. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 (51)
21. #6 AND #20 (43)
22. (#21) IN DARE (30)
23. (#21) IN HTA (2)

PROSPERO (International Prospective Register of Systematic Reviews)

Date searched: 20 February 2019.

Search strategy

#1 MeSH DESCRIPTOR Pharyngitis EXPLODE ALL TREES (29)
#2 pharyngit* (48)
#3 nasophyryngit* OR rhinopharyngit* OR epipharyngit* (3)
#4 tonsillit* OR tonsilit* (35)
#5 (sore OR pain* OR ache* OR aching OR inflam* OR infect*) ADJ3 (pharyn* or throat* OR tonsil* OR nasopharyn* OR rhinopharyn* OR epipharyn*) (105)
#6 #1 OR #2 OR #3 OR #4 OR #5 (125)
#7 strep* ADJ5 (throat* or pharyn* or tonsil*) (8)
#8 #6 OR #7 (125)

Status of review: completed or published (17).

Browsed online by information specialist: none relevant.

Trials registers

ClinicalTrials.gov

Date searched: 20 February 2019.

Search strategy

Thirty-three studies were found for:

Active, not recruiting, Completed, Suspended, Terminated, Withdrawn, Unknown status Studies | “strep throat” OR (strep OR streptococcus OR streptococcal OR “group a” OR gabhs) AND (throat OR pharynx OR tonsils) OR pharyngitis OR rhinopharyngitis OR epipharyngitis OR tonsillitis OR tonsilitis OR “sore throat” | rapid OR antigen OR radt OR radts OR rdt OR rdts OR “point of care” OR poc OR poct OR pocts OR bedside OR bed-side OR near-patient OR nearpatient OR diagnostic OR diagnosis OR test OR tests OR testing OR kit OR kits OR clearview OR veritor OR quikread OR quik-read OR alere OR cobas OR genexpert OR testpack OR test-pack OR bionexia OR bio-nexia OR biosynex OR nadal OR osom OR sofia OR xpert OR abbott OR “beckton dickinson” OR biopanda OR “nal von minden” OR sekisui OR “orion diagnostica” OR roche OR cepheid OR biomerieux OR quidel.

Downloaded to Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) and screened by an information specialist against inclusion criteria and with reference to included studies from database searches. No new studies were identified.

Conferences and professional organisations

Selected with advice from several advisors [Noel McCarthy (University of Warwick, Coventry, UK) and NICE specialist committee members].

Federation of Infection Societies conference

Date searched: 6 March 2019.

2019 November: not available yet.

2018: https://fis2018.co.uk/ (browsed abstracts > diagnostics) – 0 relevant.

2017: http://event.federationinfectionsocieties.com/ (browsed abstracts) – 0 relevant.

2016: www.journalofhospitalinfection.com/issue/S0195-6701(16)X0012-6 [searched abstracts (poster and oral presentations and invited speaker abstracts) one term at a time. Terms used: strep or group a or throat or pharyn or tonsil (search looked for these within words as well as whole words)] – 0 relevant.

2015: abstracts appear not to be available online.

2014: searched abstracts one term at a time. Terms used: strep or group a or throat or pharyn or tonsil (search looked for these within words as well as whole words) – 0 relevant.

The European Congress of Clinical Microbiology and Infectious

Date searched: 5 March 2019.

URL: www.eccmid.org/.

EMBASE indexes up to 22nd European Congress of Clinical Microbiology and Infectious Diseases, London, UK, 2012.

Older and more recent years available via the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) eLibrary: www.escmid.org/escmid_publications/escmid_elibrary/.

Searched ESCMID eLibrary on 5 March 2019 for the following terms, with no date limit.

Search strategy

strep – 25 results (three sent to reviewers).

"group a" AND streptococcus, limited to 'Topics: Diagnostic Bacteriology & General Microbiology' – 10 (one sent to reviewers).

"group a" AND streptococcal, limited to 'Topics: Diagnostic Bacteriology & General Microbiology' – 8 (one sent to reviewers).

American Society of Microbiology

American Society of Microbiology Microbes: www.asm.org/ (website restructured; past meeting abstracts unavailable).

British Society for Antimicrobial Chemotherapy

Date searched: 6 March 2019.

URL: www.bsac.org.uk.

British Society for Antimicrobial Chemotherapy spring meeting abstracts 2016–18 and general website searched one term at a time. Terms used: strep or group a or throat or pharyn or tonsil (search looked for these within words as well as whole words) – screened online; none relevant.

British Infection Association

Date searched: 6 March 2019.

URL: www.britishinfection.org/.

None relevant.

Note: British Society for Antimicrobial Chemotherapy spring conference – Thursday 21 and Friday 22 March 2019.

Public Health England Annual Conference and Public Health Research and Science Annual Conference

Date searched: 12 March 2019.

Search strategy

2016–18: https://phe.multilearning.com/phe/#!*menu=6*browseby=3*sortby=2. Searched one term at a time. Terms used: strep or streptococcal or streptococcus of group a or throat or pharyngitis or pharynx or tonsillitis or tonsilitis (search looked for whole words) – screened online; none relevant.

Streptococcal biology conference

Date searched: 12 March 2019.

URL: www.grc.org/streptococcal-biology-conference/2018/.

Search strategy

Searched one term at a time. Terms used: throat or pharyn or tonsil or rapid or point or diagnos (search looked for these within words as well as whole words) – 0 results.

Lancefield International Symposium on Streptococci and Streptococcal Diseases

Date searched: 12 March 2019.

Not indexed in EMBASE. Some abstracts indexed in Web of Science, but only up to 2009.

2017: http://lisssd2017.org/abstracts/ – website unavailable.

Not able to find a list of full abstracts for most recent 5 years online.

Microbiology Society Conference

Date searched: 12 March 2019.

2019 (abstract book for April 2019 available): https://microbiologysociety.org/event/annual-conference/annual-conference.html.

2018: https://microbiologysociety.org/event/annual-conference/annual-conference-2018.html#tab-2.

2017: https://microbiologysociety.org/events/annual-conference.html?eventYear=2017.

2016: https://microbiologysociety.org/event/annual-conference/annual-conference-2016.html.

2015: https://microbiologysociety.org/event/annual-conference/annual-conference-2015.html.

Searched one term at a time. Terms used: streptococcal or streptococcus of group a or throat or pharyn or tonsil (search looked for these within words as well as whole words) – screened online; none relevant.

Association of Clinical Biochemistry and Laboratory Medicine

Date searched: 12 March 2019.

2018 and 2019 searched.

URL: www.acb.org.uk/whatwedo/events/national_meetings.aspx.

URL: www.acb.org.uk/whatwedo/events/national_meetings/focus-2018/abstracts/posterabstracts.

Searched one term at a time. Terms used: streptococcal or streptococcus of group a or throat or pharyn or tonsil (search looked for these within words as well as whole words) – screened online; none relevant.

In addition, the website was searched using Google Advanced Search with www.acb.org.uk in the domain.

Search strategy

strep* OR throat OR tonsil* OR pharyn* OR "group a"

URL: www.acb.org.uk – seven results; screened online; none relevant.

Royal College of Pathologists

Date searched: 12 March 2019.

The website was searched using Google Advanced Search with www.acb.org.uk in the domain.

Search strategy

strep* OR throat OR tonsil* OR pharyn* OR "group a".

URL: www.rcpath.org – 55 results; screened online; none relevant.

Included studies in relevant reviews

Reviews found in searches

Vachhani *et al.*[95] focuses on manufacturers' package inserts. The report refers to the following systematic reviews in the background:

- Lean *et al.*[69] cross-checked 14 articles that mention a test name within our scope, out of the 48 total included studies. All 14 have already been picked up and sifted.
- Stewart *et al.*[96] cross-checked 58 included studies with database search results; 57 of the 58 have already been picked up and sifted. The one remaining (Parviainen *et al.*[97]) includes tests not within scope [ReaScan Strep A test (Reagena International Ltd, Toivala, Finland) vs. standard culture vs. TestPack® Strep A test (Inverness Medical, Cranfield, UK)].
- Ruiz-Aragon *et al.*[98] was not in English and older (published 2010).

Cohen *et al.*[99] included studies scanned for test names in the scope and cross-checked against the results of database searches.

Some were found that we excluded owing to not having the test name in the meeting abstract, where Cochrane reviewers contacted authors and were given more information. Sent to reviewers.

Mlejnek *et al.*:[100]

- go to characteristics of included studies: www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010502.pub2/references#characteristicStudies
- and search using ctrl + f for 'Mlejnek 2014'.

Pauchard *et al.*:[57]

- go to the same link above and search using ctrl + f for 'Pauchard 2013'.

Pauchard *et al.*:[101]

- go to the same link above and search using ctrl + f for 'Pauchard 2012'.

Not found in our searches:

Schwartz *et al.*:[102]

- letter.

Schwartz *et al.*[102]

Sedki *et al.*:[103]

- checked full text – not a test in our scope (Streptatest®, Dektra Pharm, Strasbourg, France).

Sedki *et al.*[103]

Also checked:

Banerjee and Ford.[104]

References of our included studies

Searched in March 2019 for studies.

Manufacturers' websites

Searched in January 2019 for studies and data.

Rachel Court also checked manufacturers' submissions for mention of studies. Forwarded relevant details, abstracts, posters and package inserts to reviewers.

Regulatory bodies

Food and Drug Administration, Clinical Laboratory Improvement Amendments database

Targeted searches undertaken on 6 March 2019.

Test system/manufacturer: NADAL. None found.

Test system/manufacturer: nal von minden. None found.

Test system/manufacturer: Cepheid AND Analyte Name: Streptococcus, group A. Two found, most relevant one sent to reviewers.

Test system/manufacturer: Cobas AND Analyte Name: Streptococcus, group A. Two found; earliest one sent to reviewers.

Test system/manufacturer: Biopanda. None found.

Test system/manufacturer: Biomerieux AND Analyte Name: Streptococcus, group A. None found.

Test system/manufacturer: Bionexia AND Analyte Name: Streptococcus, group A. None found.

Test system/manufacturer: Alere i AND Analyte Name: Streptococcus, group A One found (Alere i) – sent to reviewers.

Test system/manufacturer: Abbott AND Analyte Name: Streptococcus, group A. One found (TestPack Plus) – sent to reviewers.

Test system/manufacturer: Clearview AND Analyte Name: Streptococcus, group A. None found for Abbott.

Test system/manufacturer: BD Veritor AND Analyte Name: Streptococcus, group A. One found – sent to reviewers.

Test system/manufacturer: OSOM AND Analyte Name: Streptococcus, group A. Several found, but no details of studies in summaries/statements.

Test system/manufacturer: Orion Diagnostica AND Analyte Name: Streptococcus, group A. None found for QuikRead Go.

Test system/manufacturer: QuikRead Go AND Analyte Name: Streptococcus, group A. None found.

Test system/manufacturer: Biosynex. None found.

Test system/manufacturer: Quidel AND Analyte Name: Streptococcus, group A. Several found; earliest one sent to reviewers.

European commission medical devices

Checked on 6 March 2019. NB Eudamed database not yet publicly available.

Health services research agencies

International Network of Agencies for Health Technology Assessment

Date searched: 8 March 2019. HTA database also searched (see *Bibliographic databases*).

Google

Date searched: 27 February 2019.

Targeted search for NADAL Strep A scan using various terms. No study data found.

Appendix 2 Data extraction form for primary studies

Name of first reviewer: *Name of second reviewer:*

Study details	
Study ID (Endnote ref)	
First author surname	
Year of publication	
Country	
Study design	
Study setting	
Number of centres	
Study duration	
Question type	
Test accuracy (1) Other outcomes only (2)	
Aim of the study	
Patient selection	
Inclusion criteria:	
Exclusion criteria:	

Baseline characteristics/Population	
Number at baseline	
Women (%)	
Age years, median (range)	
Number with index test results included in the final analysis	
Adults (n)	
Adults aged 15 -75 y, n (%)	
Adults aged > 75 y, n (%)	
Children (n)	
Children aged 5 - 14 y, n (%)	
Number with centor score ≥3	
Number with centore score <3	
Number with FeverPAIN score ≥4	
Number with FeverPAIN score 2-3	
Number with FeverPAIN score <2	
Number with McIsaac score >2	
Co-morbidities	
Recent Abx Tx prior to study enrolment, n(%)	
Strep A prevalence in entire or target population (%)	

Index test and comparator for Strep A	
Name of index test	
Proportion of index test results validated with microbiological culture, n (%)	
Comparison with Centor score (Yes or No)	
Proportion with a centor score, n (%)	
Comparison with FeverPAIN score (Yes or No)	
Proportion with a FeverPAIN score, n (%)	
Comparison with McIsaac score (Yes or No)	
Proportion with McIsaac score, n(%)	
Reference standard	
Notes / Comments:	

Diagnostic accuracy of clinical score	
Clinical score groupings	
True positives	
False positives	
True negatives	
False negatives	
Total number	
Sensitivity (%) (95% CI)	
Specificity (%) (95% CI)	
PPV (%) (95% CI)	
NPV (%) (95% CI)	

Diagnostic accuracy of point-of-care test	
True positives	
False positives	
True negatives	
False negatives	
Total number	
Sensitivity (%) (95% CI)	
Specificity (%) (95% CI)	
PPV (%) (95% CI)	
NPV (%) (95% CI)	

Diagnostic accuracy of point-of-care test with PCR adjudication	
True positives	
False positives	
True negatives	
False negatives	
Total number	
Sensitivity (%) (95% CI)	
Specificity (%) (95% CI)	
PPV (%) (95% CI)	
NPV (%) (95% CI)	

Other outcomes	
Discordant results with standard microbiology tests	
Number of delayed or immediate Abx prescriptions used	
Contribution to antimicrobial stewardship	
Time to test results	
Test failure rate	
Time to Abx prescribing decision	
Morbidity	
Mortality	
HLQoL	
Patient or carer satisfaction with POC tests	
Healthcare professional satisfaction with test	
Any other comments:	

Appendix 3 Excluded studies with reasons

Reference	Reason for exclusion
Uphoff TS, Buchan BW, Ledeboer NA, Granato PA, Daly JA, Marti TN. Multicenter evaluation of the solana group A *Streptococcus* assay: comparison with culture. *J Clin Microbiol* 2016;**54**:2388–90. https://doi.org/10.1128/JCM.01268-16	Wrong test
Abd El-Ghany SM, Abdelmaksoud AA, Saber SM, Abd El Hamid DH. Group A beta-hemolytic streptococcal pharyngitis and carriage rate among Egyptian children: a case-control study. *Ann Saudi Med* 2015;**35**:377–82. https://doi.org/10.5144/0256-4947.2015.377	Wrong test
Abu-Sabaah AH, Ghazi HO. Better diagnosis and treatment of throat infections caused by group A beta-haemolytic streptococci. *Br J Biomed Sci* 2006;**63**:155–8. https://doi.org/10.1080/09674845.2006.11732740	Wrong test
Agarwal M, Raghuwanshi SK, Asati DP. Antibiotic use in sore throat: are we judicious? *Indian J Otolaryngol Head Neck Surg* 2015;**67**:267–70. https://doi.org/10.1007/s12070-015-0864-1	Wrong test
Alper Z, Uncu Y, Akalin H, Ercan I, Sinirtas M, Bilgel NG. Diagnosis of acute tonsillopharyngitis in primary care: a new approach for low-resource settings. *J Chemother* 2013;**25**:148–55. https://doi.org/10.1179/1973947813Y.0000000071	Wrong test
Al-Tawfiq JA, Alawami AH. A multifaceted approach to decrease inappropriate antibiotic use in a pediatric outpatient clinic. *Ann Thorac Med* 2017;**12**:51–4. https://doi.org/10.4103/1817-1737.197779	No specific RADT mentioned
Amorim R, Filho AF, Abath A, Hatem T, Mourato F, Gomes R, Mattos S. Prevalence of positive rapid antigen group A *Streptococcus* test in children and adolescents in a state from Northeast Brazil. *Cardiol Young* 2017;**27**:s484	Wrong test
Anderson KB, Simasathien S, Watanaveeradej V, Weg AL, Ellison DW, Suwanpakdee D, *et al.* Clinical and laboratory predictors of influenza infection among individuals with influenza-like illness presenting to an urban Thai hospital over a five-year period. *PLOS ONE* 2018;**13**:e0193050. https://doi.org/10.1371/journal.pone.0193050	Wrong test
Anderson NW, Buchan BW, Mayne D, Mortensen JE, Mackey TL, Ledeboer NA. Multicenter clinical evaluation of the illumigene group A *streptococcus* DNA amplification assay for detection of group A *streptococcus* from pharyngeal swabs. *J Clin Microbiol* 2013;**51**:1474–7. https://doi.org/10.1128/JCM.00176-13	Wrong test
André M, Eriksson M, Mölstad S, Stålsbylundborg C, Jacobsson A, Odenholt I, Swedish Study Group on Antibiotic Use. The management of infections in children in general practice in Sweden: a repeated 1-week diagnosis-prescribing study in 5 counties in 2000 and 2002. *Scand J Infect Dis* 2005;**37**:863–9. https://doi.org/10.1080/00365540500335207	No specific RADT mentioned
Andrews D, Chetty Y, Cooper BS, Virk M, Glass SK, Letters A, *et al.* Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use. *BMC Infect Dis* 2017;**17**:671. https://doi.org/10.1186/s12879-017-2784-z	Wrong test
Anonymous. Group A streptococcal pharyngitis: diagnosis and management. *Drug Benefit Trends* 2003;**15**:29–32	Wrong test
Aoki A, Ashizawa T, Ebata A, Nasu Y, Fujii T. Group A *streptococcus* pharyngitis outbreak among university students in a judo club. *J Infect Chemother* 2014;**20**:190–3. https://doi.org/10.1016/j.jiac.2013.10.004	Wrong test
Araujo Filho BC, Imamura R, Sennes LU, Sakae FA. Role of rapid antigen detection test for the diagnosis of group A beta-hemolytic *Streptococcus* in patients with pharyngotonsillitis. *Braz J Otorhinolaryngol* 2005;**71**:168–71	Wrong test
Araujo Filho BC, Imamura R, Sennes LU, Sakae FA. Role of rapid antigen detection test for the diagnosis of group-A beta-hemolytic *Streptococcus* in patients with pharyngotonsillitis. *Braz J Otorhinolaryngol* 2006;**72**:12–15	Wrong test

Reference	Reason for exclusion
Arbefeville S, Nelson K, Thonen-Kerr E, Ferrieri P. Prospective postimplementation study of solana group A streptococcal nucleic acid amplification test vs conventional throat culture. *Am J Clin Pathol* 2018;**150**:333–7. https://doi.org/10.1093/ajcp/aqy051	Wrong test
Armengol CE, Hendley JO, Schlager TA. Could repetition of the rapid antigen detection test for group A streptococci on a second swab replace the backup throat culture? *Pediatr Res* 2004;**55**:341A	Meeting abstract could not be located
Armengol CE, Schlager TA, Hendley JO. Sensitivity of a rapid antigen detection test for group A streptococci in a private pediatric office setting: answering the Red Book's request for validation. *Pediatrics* 2004;**113**:924–6. https://doi.org/10.1542/peds.113.4.924	Wrong test
Atlas SJ, McDermott SM, Mannone C, Barry MJ. The role of point of care testing for patients with acute pharyngitis. *J Gen Intern Med* 2005;**20**:759–61	Wrong test
Ayanruoh S, Waseem M, Quee F, Humphrey A, Reynolds T. Impact of rapid streptococcal test on antibiotic use in a pediatric emergency department. *Pediatr Emerg Care* 2009;**25**:748–50. https://doi.org/10.1097/PEC.0b013e3181bec88c	Wrong test
Balasubramanian S, Amperayani S, Dhanalakshmi K, Senthilnathan S, Chandramohan V. Rapid antigen diagnostic testing for the diagnosis of group A beta-haemolytic streptococci pharyngitis. *Natl Med J India* 2018;**31**:8–10. https://doi.org/10.4103/0970-258X.243433	Wrong test
Ba-Saddik IA, Munibari AA, Alhilali AM, Ismail SM, Murshed FM, Coulter JB, *et al.* Prevalence of Group A beta-haemolytic *streptococcus* isolated from children with acute pharyngotonsillitis in Aden, Yemen. *Trop Med Int Health* 2014;**19**:431–9. https://doi.org/10.1111/tmi.12264	Wrong test
Bergmark R, Bergmark B, Blander J, Fataki M, Janabi M. Burden of disease and barriers to the diagnosis and treatment of group A beta-hemolytic streptococcal pharyngitis for the prevention of rheumatic heart disease in Dar Es Salaam, Tanzania. *Pediatr Infect Dis J* 2010;**29**:1135–7. https://doi.org/10.1097/inf.0b013e3181edf475	No specific RADT mentioned
Bjerrum L, Cots JM, Llor C, Molist N, Munck A. Effect of intervention promoting a reduction in antibiotic prescribing by improvement of diagnostic procedures: a prospective, before and after study in general practice. *Eur J Clin Pharmacol* 2006;**62**:913–18. https://doi.org/10.1007/s00228-006-0187-y	No comparison with biological culture or clinical scores
Brennan-Krohn T, Ozonoff A, Sandora TJ. Adherence to guidelines for testing and treatment of children with pharyngitis: a retrospective study. *BMC Pediatr* 2018;**18**:43. https://doi.org/10.1186/s12887-018-0988-z	No specific RADT mentioned
Briel M, Young J, Tschudi P, Hersberger KE, Hugenschmidt C, Langewitz W, Bucher HC. Prevalence and influence of diagnostic tests for acute respiratory tract infections in primary care. *Swiss Med Wkly* 2006;**136**:248–53	Wrong population
Brittain-Long R, Westin J, Olofsson S, Lindh M, Andersson LM. Access to a polymerase chain reaction assay method targeting 13 respiratory viruses can reduce antibiotics: a randomised, controlled trial. *BMC Med* 2011;**9**:44. https://doi.org/10.1186/1741-7015-9-44	No specific RADT mentioned
Brook I, Gober AE. Concurrent influenza A and group A beta-hemolytic streptococcal pharyngotonsillitis. *Ann Otol Rhinol Laryngol* 2008;**117**:310–12. https://doi.org/10.1177/000348940811700412	Wrong test
Bursle E, Robson J. Non-culture methods for detecting infection. *Aust Prescr* 2016;**39**:171–5. https://doi.org/10.18773/austprescr.2016.059	Review
Camurdan AD, Camurdan OM, Ok I, Sahin F, Ilhan MN, Beyazova U. Diagnostic value of rapid antigen detection test for streptococcal pharyngitis in a pediatric population. *Int J Pediatr Otorhinolaryngol* 2008;**72**:1203–6. https://doi.org/10.1016/j.ijporl.2008.04.008	Wrong test
Cao C, Zhang F, Ji M, Pei F, Fan X, Shen H, *et al.* Development of a loop-mediated isothermal amplification method for rapid detection of streptococcal pyrogenic exotoxin B. *Toxicon* 2016;**117**:53–8. https://doi.org/10.1016/j.toxicon.2016.03.019	No specific RADT mentioned

Reference	Reason for exclusion
Cardoso DM, Gilio AE, Hsin SH, Machado BM, de Paulis M, Lotufo JP, *et al.* Impact of the rapid antigen detection test in diagnosis and treatment of acute pharyngotonsillitis in a pediatric emergency room. *Rev Paul Pediatr* 2013;**31**:4–9	No comparison with biological culture or clinical scores
Chen FM. Culture confirmation of negative rapid strep test results. *J Fam Pract* 2000;**49**:371–2	Wrong test
Cheng C, Han B, Smoot B, Chen Y, Exner MM. Real-time PCR detection of group A *Streptococcus* using the 3M integrated cycler. *J Mol Diagn* 2010;**12**:883	Wrong test
Cohen JF, Chalumeau M, Levy C, Bidet P, Benani M, Koskas M, *et al.* Effect of clinical spectrum, inoculum size and physician characteristics on sensitivity of a rapid antigen detection test for group A streptococcal pharyngitis. *Eur J Clin Microbiol Infect Dis* 2013;**32**:787–93. https://doi.org/10.1007/s10096-012-1809-1	Wrong test
Cohen JF, Chalumeau M, Levy C, Bidet P, Thollot F, Wollner A, *et al.* Spectrum and inoculum size effect of a rapid antigen detection test for group A *Streptococcus* in children with pharyngitis. *PLOS ONE* 2012;**7**:e39085. https://doi.org/10.1371/journal.pone.0039085	Wrong test
Cohen JF, Cohen R, Bidet P, Elbez A, Levy C, Bossuyt PM, Chalumeau M. Efficiency of a clinical prediction model for selective rapid testing in children with pharyngitis: a prospective, multicenter study. *PLOS ONE* 2017;**12**:e0172871. https://doi.org/10.1371/journal.pone.0172871	Wrong test
Cohen JF, Cohen R, Bidet P, Levy C, Deberdt P, d'Humières C, *et al.* Rapid-antigen detection tests for group A streptococcal pharyngitis: revisiting false-positive results using polymerase chain reaction testing. *J Pediatr* 2013;**162**:1282–4, 1284.e1. https://doi.org/10.1016/j.jpeds.2013.01.050	Wrong test
Cohen R, Levy C, Ovetchkine P, Boucherat M, Weil-Olivier C, Gaudelus J, *et al.* Evaluation of streptococcal clinical scores, rapid antigen detection tests and cultures for childhood pharyngitis. *Eur J Pediatr* 2004;**163**:281–2. https://doi.org/10.1007/s00431-004-1416-y	Wrong test
Dagnelie CF, Bartelink ML, van der Graaf Y, Goessens W, de Melker RA. Towards a better diagnosis of throat infections (with group A beta-haemolytic *Streptococcus*) in general practice. *Br J Gen Pract* 1998;**48**:959–62	Wrong test
Dale JC, Novak R, Higgens P, Wahl E. Testing for group A streptococci. *Arch Pathol Lab Med* 2002;**126**:1467–70. https://doi.org/10.1043/0003-9985(2002)126<1467:TFGAS>2.0.CO;2	No specific RADT mentioned
Dawson ED, Taylor AW, Smagala JA, Rowlen KL. Molecular detection of *Streptococcus pyogenes* and *Streptococcus dysgalactiae* subsp. *equisimilis*. *Mol Biotechnol* 2009;**42**:117–27. https://doi.org/10.1007/s12033-009-9143-2	Wrong test
Demoré B, Tebano G, Gravoulet J, Wilcke C, Ruspini E, Birge J, *et al.* 'Rapid antigen test use for the management of group A streptococcal pharyngitis in community pharmacies.' *Eur J Clin Microbiol Infect Dis* 2018;**06**:06	Wrong test
Deniz R, Aktaş E, Barış A, Bayraktar B. The use of rapid antigen testing and matrix-assisted laser desorption/ionization-time of flight mass spectrometry in the diagnosis of group A beta-hemolytic streptococci in throat swab samples *Turk J Med Sci* 2018;**48**:939–44. https://doi.org/10.3906/sag-1712-101	Wrong test
Dodd M, Adolphe A, Parada A, Brett M, Culbreath K, Mercier RC. Clinical impact of a rapid streptococcal antigen test on antibiotic use in adult patients. *Diagn Microbiol Infect Dis* 2018;**91**:339–44	Wrong test
Donato LJ, Myhre NK, Murray MA, McDonah MR, Myers JF, Maxson JA, *et al.* Assessment of test performance and potential for environmental contamination associated with a point-of-care molecular assay for group A *Streptococcus* in an end user setting. *J Clin Microbiol* 2019;**57**:e01629–18	No comparison with culture or clinical scores
Dulaney K, Hohmeier K, Fisher C, Cardosi L, Wasson M. Exploring pharmacists' perceptions regarding influenza and streptococcal testing within a chain pharmacy. *J Am Pharm Assoc* 2018;**58**:438–41.e1	No specific RADT mentioned. No comparison with culture or clinical scores
Dut R, Kocagoz S. Use of streptococcal tonsillopharyngitis diagnostic tests in children. *J Pediatric Infect Dis* 2016;**11**:126–30	Wrong test

Reference	Reason for exclusion
Dut R, Kocagöz S. Clinical signs and diagnostic tests in acute respiratory infections. *Indian J Pediatr* 2016;**83**:380–5. https://doi.org/10.1007/s12098-015-1943-8	No specific RADT mentioned
Edin A, Granholm S, Koskiniemi S, Allard A, Sjöstedt A, Johansson A. Development and laboratory evaluation of a real-time PCR assay for detecting viruses and bacteria of relevance for community-acquired pneumonia. *J Mol Diagn* 2015;**17**:315–24. https://doi.org/10.1016/j.jmoldx.2015.01.005	No specific RADT mentioned
Edmonson MB, Farwell KR. Relationship between the clinical likelihood of group A streptococcal pharyngitis and the sensitivity of a rapid antigen-detection test in a pediatric practice. *Pediatrics* 2005;**115**:280–5	Wrong type of test
Edmonson MB, Weix KR. Relationship of pre-test likelihood of group A streptococcal (GAS) pharyngitis and sensitivity of a rapid antigen detection test (RADT) in pediatric practice. *Pediatr Res* 2003;**53**:180A	Abstract could not be located
Ehrlich JE, Demopoulos BP, Daniel KR, Ricarte MC, Glied S. Cost-effectiveness of treatment options for prevention of rheumatic heart disease from Group A streptococcal pharyngitis in a pediatric population. *Prev Med* 2002;**35**:250–7	Wrong test name
Ehsanipour F, Mirghorbani M, Masoumi Asl H, Harandi NV, Khanaliha K. Comparison of clinical findings and rapid streptococcal antigen detection test in the diagnosis of group A streptococcal (GAS) pharyngitis. *Arch Clin Infect Dis* 2016;**11**	Wrong test
Elf S, Olli J, Hirvonen S, Auvinen P, Eboigbodin KE. Molecular detection of *Streptococcus pyogenes* by strand invasion based amplification assay. *Mol Diagn Ther* 2018;**22**:595–602. https://doi.org/10.1007/s40291-018-0346-8	Wrong type of test
Elmas B, Köroğlu M, Terzi HA, Aslan FG, Menekşe E, Kösecik M, Altindiş M. Performance of clinical features, acute phase reactants and group A *streptococcus* rapid test in evaluation of the etiologic agents for tonsillopharyngitis in children. *Clin Lab* 2017;**63**:1223–31. https://doi.org/10.7754/Clin.Lab.2017.170124	Wrong test
Engström S, Mölstad S, Lindström K, Nilsson G, Borgquist L. Excessive use of rapid tests in respiratory tract infections in Swedish primary health care. *Scand J Infect Dis* 2004;**36**:213–18. https://doi.org/10.1080/00365540310018842	No comparison with clinical score or throat culture
Enright K, Taheri S, Beattie T. Emergency department testing for *streptococcus* in children with sore throats. *Emerg Med J* 2009;**26**:310. https://doi.org/10.1136/emj.2008.058628	No specific RADT mentioned
Fakih MG, Berschback J, Juzych NS, Massanari RM. Compliance of resident and staff physicians with IDSA guidelines for the diagnosis and treatment of streptococcal pharyngitis. *Infect Dis Clin Pract* 2006;**14**:84–8	Wrong test
FDA. *FDA Decision Summary: Substantial Equivalence Determination for the Sofia® Strep A + FIA. K141775*. Silver Spring, MD: FDA; 2014. URL: www.accessdata.fda.gov/cdrh_docs/reviews/K141775.pdf (accessed 6 March 2019)	Wrong test
FDA. *FDA Decision Summary: Substantial Equivalence Determination for Cobas Liat Strep A. K141338*. Silver Spring, MD: FDA; 2015. URL: www.accessdata.fda.gov/cdrh_docs/reviews/K141338.pdf (accessed 6 March 2019)	Data identical to those provided by the manufacturer in response to a request for information by NICE
FDA. *FDA Decision Summary: Substantial Equivalence Determination for TestPack Plus Strep A. K971522*. Silver Spring, MD: FDA; 1997. URL: www.accessdata.fda.gov/cdrh_docs/pdf/K971522.pdf (accessed 6 March 2019)	Insufficient information
Felsenstein S, Faddoul D, Sposto R, Batoon K, Polanco CM, Dien Bard J. Molecular and clinical diagnosis of group A streptococcal pharyngitis in children. *J Clin Microbiol* 2014;**52**:3884–9. https://doi.org/10.1128/JCM.01489-14	Wrong test
Fierro JL, Prasad PA, Localio AR, Grundmeier RW, Wasserman RC, Zaoutis TE, Gerber JS. Variability in the diagnosis and treatment of group A streptococcal pharyngitis by primary care pediatricians. *Infect Control Hosp Epidemiol* 2014;**35**(Suppl. 3):79–85. https://doi.org/10.1086/677820	No specific RADT mentioned
Fontes MJ, Bottrel FB, Fonseca MT, Lasmar LB, Diamante R, Camargos PA. Early diagnosis of streptococcal pharyngotonsillitis: assessment by latex particle agglutination test. *J Pediatr* 2007;**83**:465–70. https://doi.org/10.2223/JPED.1695	Wrong type of test

Reference	Reason for exclusion
Forward K. Just the berries. Diagnosing and managing group A *Streptococcus* pharyngitis. *Can Fam Physician* 2002;**48**:47–8	Review
Forward KR, Haldane D, Webster D, Mills C, Brine C, Aylward D. A comparison between the Strep A Rapid Test Device and conventional culture for the diagnosis of streptococcal pharyngitis. *Can J Infect Dis Med Microbiol* 2006;**17**:221–3	Wrong test
Fox JW, Cohen DM, Marcon MJ, Cotton WH, Bonsu BK. Performance of rapid streptococcal antigen testing varies by personnel. *J Clin Microbiol* 2006;**44**:3918–22	Wrong test
Fox JW, Marcon MJ, Bonsu BK. Diagnosis of streptococcal pharyngitis by detection of *Streptococcus pyogenes* in posterior pharyngeal versus oral cavity specimens. *J Clin Microbiol* 2006;**44**:2593–4	Wrong test
Gazewood J. Negative antigen test misses < 5% of strep pharyngitis. *J Fam Pract* 2003;**52**:761–2	Review
Gazzano V, Berger A, Benito Y, Freydiere AM, Tristan A, Boisset S, *et al.* Reassessment of the role of rapid antigen detection tests in diagnosis of invasive group A streptococcal infections. *J Clin Microbiol* 2016;**54**:994–9. https://doi.org/10.1128/JCM.02516-15	Wrong population
Gieseker KE, Roe MH, MacKenzie T, Todd JK. Evaluating the American Academy of Pediatrics diagnostic standard for *Streptococcus pyogenes* pharyngitis: backup culture versus repeat rapid antigen testing. *Pediatrics* 2003;**111**:e666–70	Wrong test
Gieseker KE, Mackenzie T, Roe MH, Todd JK. Comparison of two rapid *Streptococcus pyogenes* diagnostic tests with a rigorous culture standard. *Pediatr Infect Dis J* 2002;**21**:922–7. https://doi.org/10.1097/00006454-200210000-00007	Wrong test
Giraldez-Garcia C, Rubio B, Gallegos-Braun JF, Imaz I, Gonzalez-Enriquez J, Sarria-Santamera A. Diagnosis and management of acute pharyngitis in a paediatric population: a cost-effectiveness analysis. *Eur J Pediatr* 2011;**170**:1059–67. https://doi.org/10.1007/s00431-011-1410-0	No specific RADT mentioned
Gonsu HK, Bomki CM, Djomou F, Toukam M, Ndze VN, Lyonga EE, *et al.* A comparative study of the diagnostic methods for group A streptococcal sore throat in two reference hospitals in Yaounde, Cameroon. *Pan Afr Med J* 2015;**20**:139. https://doi.org/10.11604/pamj.2015.20.139.4810	Wrong test
Greiver M. Practice tips. Incorporating a rapid group A streptococcus assay with the sore throat score. *Can Fam Physician* 1999;**45**:1181–2	Review
Gröndal H, Hedin K, Strandberg EL, André M, Brorsson A. Near-patient tests and the clinical gaze in decision-making of Swedish GPs not following current guidelines for sore throat - a qualitative interview study. *BMC Fam Pract* 2015;**16**:81. https://doi.org/10.1186/s12875-015-0285-y	No specific RADT mentioned
Gurol Y, Akan H, Izbirak G, Tekkanat ZT, Gunduz TS, Hayran O, Yilmaz G. The sensitivity and the specifity of rapid antigen test in streptococcal upper respiratory tract infections. *Int J Pediatr Otorhinolaryngol* 2010;**74**:591–3. https://doi.org/10.1016/j.ijporl.2010.02.020	Wrong test
Haldrup S, Thomsen RW, Bro F, Skov R, Bjerrum L, Søgaard M. Microbiological point of care testing before antibiotic prescribing in primary care: considerable variations between practices. *BMC Fam Pract* 2017;**18**:9. https://doi.org/10.1186/s12875-016-0576-y	No specific RADT mentioned
Hall MC, Kieke B, Gonzales R, Belongia EA. Spectrum bias of a rapid antigen detection test for group A beta-hemolytic streptococcal pharyngitis in a pediatric population. *Pediatrics* 2004;**114**:182–6. https://doi.org/10.1542/peds.114.1.182	Wrong test
Hammond-Collins K, Strauss B, Barnes K, Demczuk W, Domingo MC, Lamontagne MC, *et al.* Group A *streptococcus* outbreak in a Canadian armed forces training facility. *Mil Med* 2018;**21**:21	Wrong test
Herranz B, Rodriguez-Salinas E, Orden B. [From laboratory to clinic: usefulness of rapid diagnostic techniques for the diagnostic techniques of *Streptococcus pyogenes*.] *An Pediatr Contin* 2007;**5**:92–5	Foreign-language paper
Hinfey P, Nicholls BH, Garcia F, Ripper J, Cameron Y, Joshi S. Sensitivity of a rapid antigen detection test for the diagnosis of group A streptococcal pharyngitis in the emergency department. *Ann Emerg Med* 2010;**56**:S132	Wrong test

Reference	Reason for exclusion
Hoffmann K, Reichardt B, Zehetmayer S, Maier M. Evaluation of the implementation of a rapid streptococcal antigen test in a routine primary health care setting: from recommendations to practice. *Wien Klin Wochenschr* 2012;**124**:633–8. https://doi.org/10.1007/s00508-012-0225-y	No specific RADT mentioned
Homme JH, Greenwood CS, Cronk LB, Nyre LM, Uhl JR, Weaver AL, Patel R. Duration of group A *streptococcus* PCR positivity following antibiotic treatment of pharyngitis. *Diagn Microbiol Infect Dis* 2018;**90**:105–8	Wrong test
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Joachim L, Campos D, Smeesters PR. Pragmatic scoring system for pharyngitis in low-resource settings. *Pediatrics* 2010;**126**:e608–14. https://doi.org/10.1542/peds.2010-0569	Wrong test
Kato Y, Suzuki K, Shibai Y, Iwamoto H. Development of simultaneous detection lateral flow immunoassay kit for GAS and ADV. *Clin Chem* 2015;**1**:S150	Wrong test
Keahey L, Bulloch B, Jacobson R, Tenenbein M, Kabani A. Diagnostic accuracy of a rapid antigen test for GABHS performed by nurses in a pediatric ED. *Am J Emerg Med* 2002;**20**:128–30	Wrong test
Khattak MH, Khan MA, Shafiullah Orakzi UK. Incidence of acute streptococcal pharyngitis. *J Med Sci* 2015;**23**:118–20	No specific RADT mentioned
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Kurtz B, Kurtz M, Roe M, Todd J. Importance of inoculum size and sampling effect in rapid antigen detection of *Streptococcus pyogenes* pharyngitis. *Pediatr Res* 1999;**45**:166A	Not enough information
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Leydon GM, McDermott L, Moore M, Williamson I, Hobbs FD, Lambton T, *et al.* A qualitative study of GP, NP and patient views about the use of rapid streptococcal antigen detection tests (RADTs) in primary care: 'swamped with sore throats?'. *BMJ Open* 2013;**3**:e002460. https://doi.org/10.1136/bmjopen-2012-002460	No specific RADT mentioned
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Llor C, Moragas A, Cots JM, López-Valcárcel BG, Happy Audit Study Group. Estimated saving of antibiotics in pharyngitis and lower respiratory tract infections if general practitioners used rapid tests and followed guidelines. *Aten Primaria* 2017;**49**:319–25	No specific RADT mentioned
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Mazur E, Bochyńska E, Juda M, Kozioł-Montewka M. Empirical validation of Polish guidelines for the management of acute streptococcal pharyngitis in children. *Int J Pediatr Otorhinolaryngol* 2014;**78**:102–6. https://doi.org/10.1016/j.ijporl.2013.10.064	Wrong test
Messina A, Bottaro G, Morselli I. Utility of rapid antigen detection test for group A streptococci in a family paediatrician office setting. *Acta Med Mediterr* 2010;**26**:101–5	No outcomes by test
Michel-Lepage A, Ventelou B, Nebout A, Verger P, Pulcini C. Cross-sectional survey: risk-averse French GPs use more rapid-antigen diagnostic tests in tonsillitis in children. *BMJ Open* 2013;**3**:e003540. https://doi.org/10.1136/bmjopen-2013-003540	No specific RADT mentioned
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Mirza A, Wludyka P, Chiu TT, Rathore MH. Throat culture is necessary after negative rapid antigen detection tests. *Clin Pediatr* 2007;**46**:241–6	Wrong test
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Moore N. Rapid and sensitive isothermal molecular amplification of group A *Streptococcus* (GAS) with Alere i Molecular Platform. *J Molec Diagnos* 2017;**19**:987	Wrong outcome
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NCT. *Performance of Ellume·Lab Group A Strep Test Versus Culture for the Rapid Detection of Group A* Streptococcus *in Patients with Acute Pharyngitis*. 2017. URL: https://clinicaltrials.gov/show/nct03171350 (accessed 20 February 2019)	No study publication. No results
NCT. *Comparison of Two Rapid Antigen Detection Tests for the Detection of Group-A Streptococcal Pharyngitis in Children*. 2017. URL: https://clinicaltrials.gov/show/nct03099018 (accessed 20 February 2019)	No outcome data
Neumark T, Brudin L, Molstad S. Use of rapid diagnostic tests and choice of antibiotics in respiratory tract infections in primary healthcare – a 6-y follow-up study. *Scand J Infect Dis* 2010;**42**:90–6	No specific RADT mentioned
Nissinen A, Strandén P, Myllys R, Takkinen J, Björkman Y, Leinikki P, Siitonen A. Point-of-care testing of group A streptococcal antigen: performance evaluated by external quality assessment. *Eur J Clin Microbiol Infect Dis* 2009;**28**:17–20. https://doi.org/10.1007/s10096-008-0580-9	No comparison with culture or clinical score
Noorbakhsh S, Tabatabaei A, Farhadi M, Ebrahimi TF. Immunoasssay chromatographic antigen test for rapid diagnosis of Group A beta hemolytic *streptococcus* pharyngitis in children: a cross/sectional study. *Iran J Microbiol* 2011;**3**:99–103	Wrong test
Orda U, Mitra B, Orda S, Fitzgerald M, Gunnarsson R, Rofe G, Dargan A. Point of care testing for group A streptococci in patients presenting with pharyngitis will improve appropriate antibiotic prescription. *Emerg Med Australas* 2016;**28**:199–204. https://doi.org/10.1111/1742-6723.12567	Wrong reference standard
Orda U, Gunnarsson R, Orda S, Fitzgerald M, Rofe G, Dargan A. Etiologic predictive value of a rapid immunoassay for the detection of group A *streptococcus* antigen from throat swabs in patients presenting with a sore throat. *Int J Infect Dis* 2016;**45**:32–5. https://doi.org/10.1016/j.ijid.2016.02.002	No comparison with culture or clinical score
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Papastergiou J, Trieu CR, Saltmarche D, Diamantouros A. Community pharmacist-directed point-of-care group A *streptococcus* testing: evaluation of a Canadian program. *J Am Pharm Assoc* 2018;**58**:450–6	No comparison with culture or clinical score
Park SY, Gerber MA, Tanz RR, Hickner JM, Galliher JM, Chuang I, Besser RE. Clinicians' management of children and adolescents with acute pharyngitis. *Pediatrics* 2006;**117**:1871–8	No specific RADT mentioned
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Phung E, Mirzaian E, Arouchanova D. Utilization of pharmacist-performed rapid influenza and group A *Streptococcus* testing and treatment in the community pharmacy setting: economic value and patient satisfaction. *J Am Pharm Assoc* 2018;**58**:e129	Abstract only. No extractable data
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Plainvert C, Duquesne I, Touak G, Dmytruk N, Poyart C. In vitro evaluation and comparison of 5 rapid antigen detection tests for the diagnosis of beta-hemolytic group A streptococcal pharyngitis. *Diagn Microbiol Infect Dis* 2015;**83**:105–11. https://doi.org/10.1016/j.diagmicrobio.2015.06.012	Wrong population
Pulcini C, Pauvif L, Paraponaris A, Verger P, Ventelou B. Perceptions and attitudes of French general practitioners towards rapid antigen diagnostic tests in acute pharyngitis using a randomised case-vignette study: a cross-sectional study. *Clin Microbiol Infect* 2012;**3**:494	No specific RADT mentioned
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Ramos JL, Fraile MT, Chanza M, Tormo N, Lurbe A, Gimeno C. Rapid detection of *Streptococcus pyogenes* in peripheral medical centres. A pilot custody assay. *Clin Microbiol Infect* 2011;**4**:S250	Wrong test
Rao A, Berg B, Quezada T, Fader R, Walker K, Tang S, *et al.* Diagnosis and antibiotic treatment of group A streptococcal pharyngitis in children in a primary care setting: impact of point-of-care polymerase chain reaction. *BMC Pediatr* 2019;**19**:24. https://doi.org/10.1186/s12887-019-1393-y	Wrong reference standard and no comparison with clinical score
Rathi SK, Ahmed R. Pakistan prevalence survey in acute pharyngitis. *J Pak Med Assoc* 2014;**64**:928–31	Wrong test
Rimoin AW, Vince A, Hamza H, da Cunha ALA, Chitale R, Oazi S, Steinhoff MC. Evaluation of a rapid test for streptococcal pharyngitis in children in 3 countries. *Pediatr Res* 2004;**55**:279A	Meeting abstract could not be located
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Russo ME, Kline J, Jaggi P, Leber AL, Cohen DM. The challenge of patient notification and the work of follow-up generated by a 2-step testing protocol for group A streptococcal pharyngitis in the pediatric emergency department. *Pediatr Emerge Care* 2017;**30**:30	No comparison with throat score or culture
Sancho A, Diaz-Almiron M, Yebra J, Hawkins M. S. pyogenes reviewed in a paediatric population: age and predictive models. *Arch Dis Child* 2014;**2**:A325	No specific RADT mentioned
Sarikaya S, Aktaş C, Ay D, Cetin A, Celikmen F. Sensitivity and specificity of rapid antigen detection testing for diagnosing pharyngitis in the emergency department. *Ear Nose Throat J* 2010;**89**:180–2	Wrong test
Sayyahfar S, Fahimzad A, Naddaf A, Tavassoli S. Antibiotic susceptibility evaluation of group A *streptococcus* isolated from children with pharyngitis: a study from Iran. *Infect Chemother* 2015;**47**:225–30. https://doi.org/10.3947/ic.2015.47.4.225	Wrong type of test
Scheel A, DeWyer A, Sarnacki R, Kamarembo J, Okello E, Beaton A. The utility of existing clinical decision rules for streptococcal pharyngitis in Ugandan school children. *Global Heart* 2018;**13**:508–9	No specific RADT mentioned
Schwartz RH, Kim D, Martin M, Pichichero ME. A Reappraisal of the minimum duration of antibiotic treatment before approval of return to school for children with streptococcal pharyngitis. *Pediatr Infect Dis J* 2015;**34**:1302–4. https://doi.org/10.1097/INF.0000000000000883	Wrong test
Schwartz K, Monsur J, Northrup J, West P, Neale AV. Pharyngitis clinical prediction rules: effect of interobserver agreement: a MetroNet study. *J Clin Epidemiol* 2004;**57**:142–6. https://doi.org/10.1016/S0895-4356(03)00249-X	Wrong test
Shapiro DJ, Lindgren CE, Neuman MI, Fine AM. Viral features and testing for streptococcal pharyngitis. *Pediatrics* 2017;**139**:e20163403	No specific RADT mentioned
Sheeler RD, Houston MS, Radke S, Dale JC, Adamson SC. Accuracy of rapid strep testing in patients who have had recent streptococcal pharyngitis. *J Am Board Fam Pract* 2002;**15**:261–5	Wrong population

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Singh S, Dolan JG, Centor RM. Optimal management of adults with pharyngitis – a multi-criteria decision analysis. *BMC Med Inform Decis Mak* 2006;**6**:14	No specific RADT mentioned
Skoog G, Edlund C, Giske CG, Mölstad S, Norman C, Sundvall PD, Hedin K. A randomized controlled study of 5 and 10 days treatment with phenoxymethylpenicillin for pharyngotonsillitis caused by *Streptococcus* group A – a protocol study. *BMC Infect Dis* 2016;**16**:484. https://doi.org/10.1186/s12879-016-1813-7	No specific RADT mentioned
Slinger R, Goldfarb D, Rajakumar D, Moldovan I, Barrowman N, Tam R, Chan F. Rapid PCR detection of group A *streptococcus* from flocked throat swabs: a retrospective clinical study. *Ann Clin Microbiol Antimicrob* 2011;**10**:33. https://doi.org/10.1186/1476-0711-10-33	Wrong type of test
St Sauver JL, Weaver AL, Orvidas LJ, Jacobson RM, Jacobsen SJ. Population-based prevalence of repeated group A beta-hemolytic streptococcal pharyngitis episodes. *Mayo Clin Proc* 2006;**81**:1172–6	Wrong test
Subashini B, Anandan S, Balaji V. Evaluation of a rapid antigen detection test for the diagnosis of group-A beta-hemolytic *streptococcus* in pharyngotonsillitis. *J Glob Infect Dis* 2015;**7**:91–2. https://doi.org/10.4103/0974-777X.154447	Letter
Sultan AM, Seliem WA. Evaluating the use of dedicated swab for rapid antigen detection testing in group A streptococcal pharyngitis in children. *Afr J Clin Exp Microbiol* 2018;**19**:24–9	Wrong test
Supon PA, Tunnell S, Greene M, Ostroff RM. Rapid detection of group A streptococcal antigen with a new optical immunoassay. *Pediatr Infect Dis J* 1998;**17**:349–51. https://doi.org/10.1097/00006454-199804000-00019	Wrong test
Syriopoulou T, Konstantelos D, Papoula M, Karachanidi E, Maggana I, Straka K, *et al.* Laboratory methods for diagnosing streptococcal pharyngitis: predictive value, usefulness. *Clin Biochem* 2011;**44**:534–5	No specific RADT mentioned
Tanz RR, Gerber MA, Kabat W, Rippe J, Seshadri R, Shulman ST. Performance of a rapid antigen-detection test and throat culture in community pediatric offices: implications for management of pharyngitis. *Pediatrics* 2009;**123**:437–44. https://doi.org/10.1542/peds.2008-0488	Wrong test
Tanz RR, Zheng XT, Carter DM, Steele MC, Shulman ST. Caution needed: molecular diagnosis of pediatric group A streptococcal pharyngitis. *J Pediatric Infect Dis Soc* 2018;**7**:e145–e147. https://doi.org/10.1093/jpids/pix086	Wrong test
Teratani Y, Hagiya H, Koyama T, Ohshima A, Zamami Y, Tatebe Y, *et al.* Association between rapid antigen detection tests and antibiotics for acute pharyngitis in Japan: a retrospective observational study. *J Infect Chemother* 2019;**25**:267–72	No specific RADT mentioned
Thamlikitkul V, Rachata T, Popum S, Chinswangwatanakul P, Srisomnuek A, Seenama C, *et al.* Accuracy and utility of rapid antigen detection tests for group A beta-hemolytic *Streptococcus* on ambulatory adult patients with sore throat associated with acute respiratory infections at Siriraj Hospital. *J Med Assoc Thai* 2018;**101**	Wrong test
Toepfner N, Henneke P, Berner R, Hufnagel M. Impact of technical training on rapid antigen detection tests (RADT) in group A streptococcal tonsillopharyngitis. *Eur J Clin Microbiol Infect Dis* 2013;**32**:609–11. https://doi.org/10.1007/s10096-012-1783-7	Wrong test
Tsevat J, Kotagal UR. Management of sore throats in children: a cost-effectiveness analysis. *Arch Pediatr Adolesc Med* 1999;**153**:681–8. https://doi.org/10.1001/archpedi.153.7.681	Wrong test
Tsung LY, Choi KC, Nelson EA, Chan PK, Sung RY. Factors associated with length of hospital stay in children with respiratory disease. *Hong Kong Med J* 2010;**16**:440–6	Wrong type of test
Tsutsumi H, Ouchi K, Ohsaki M, Yamanaka T, Kuniya Y, Takeuchi Y, *et al.* Immunochromatography test for rapid diagnosis of adenovirus respiratory tract infections: comparison with virus isolation in tissue culture. *J Clin Microbiol* 1999;**37**:2007–9	Wrong type of test
Upton A, Lowe C, Stewart J, Taylor S, Lennon D. In vitro comparison of four rapid antigen tests for group A *Streptococcus* detection. *N Z Med J* 2014;**127**:77–83	Wrong population. No comparison with culture or clinical score

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Van Howe RS, Kusnier LP. Diagnosis and management of pharyngitis in a pediatric population based on cost-effectiveness and projected health outcomes. *Pediatrics* 2006;**117**:609–19	No specific RADT mentioned
Van Limbergen J, Kalima P, Taheri S, Beattie TF. *Streptococcus* A in paediatric accident and emergency: are rapid streptococcal tests and clinical examination of any help? *Emerge Med J* 2006;**23**:32–4	Wrong test
Vedia C, Garcia JA, Valles R, Franzi A, Morales C, Prat N. Is it possible to decrease antibiotic prescription in pediatrics? *Basic Clin Pharmacol Toxicol* 2016;**119**(Suppl. 1):47	No specific RADT mentioned
Waseem M, Ayanruoh S, Humphrey A, Reynolds T. Impact of rapid streptococcal test on antibiotic use in a pediatric emergency department. *Ann Emerg Med* 2009;**1:**S41	No specific RADT mentioned
Webb KH, Needham CA, Kurtz SR. Use of a high-sensitivity rapid strep test without culture confirmation of negative results: 2 years' experience. *J Fam Pract* 2000;**49**:34–8	Wrong test
Williams KM, Jackson MA, Hamilton M. Rapid diagnostic testing for URIs in children: impact on physician decision making and costs. *Infect Med* 2002;**19**:109–17	No empirical data
Wong MC, Chung CH. Group A streptococcal infection in patients presenting with a sore throat at an accident and emergency department: prospective observational study. *Hong Kong Med J* 2002;**8**:92–8	Wrong test
Woodburn JD, Smith KL, Nelson GD. Quality of care in the retail health care setting using national clinical guidelines for acute pharyngitis. *Am J Med Qual* 2007;**22**:457–62	Wrong test
Wright M, Williams G, Ludeman L. Comparison of two rapid tests for detecting group A streptococcal pharyngitis in the pediatric population at wright-patterson air force base. *Mil Med* 2007;**172**:644–6. https://doi.org/10.7205/milmed.172.6.644	Wrong test
Xu J, Schwartz K, Monsur J, Northrup J, Neale AV. Patient-clinician agreement on signs and symptoms of 'strep throat': a MetroNet study. *Fam Pract* 2004;**21**:599–604	Wrong test
Yang JH, Huang PY, Shie SS, Yang S, Tsao KC, Wu TL, *et al.* Diagnostic performance of the Sofia® influenza A + B fluorescent immunoassay in adult outpatients in Northern Taiwan. *J Med Virol* 2018;**90**:1010–18. https://doi.org/10.1002/jmv.25043	Wrong test
Yoon J, Yun SG, Nam J, Choi SH, Lim CS. The use of saliva specimens for detection of influenza A and B viruses by rapid influenza diagnostic tests. *J Virol Methods* 2017;**243**:15–19	Wrong test

Appendix 4 The QUADAS-2 tailored guidance notes and form

Modified QUADAS-2 and guidance notes for strep A

Risk of bias should only be classed as low for each domain if all questions could be answered with 'yes'. If one or more signalling question is answered with 'no' the risk of bias should be classed as 'high' and equally if at least one question is answered with 'unclear' the risk of bias should be judged 'unclear'.

Domain 1: patient selection

Test measurement ratings will differ depending on whether or not antibiotics have been previously prescribed.

A. Risk of bias

Guidance

Was a consecutive or random sample of patients enrolled?
This question should only be answered with 'yes' if the study clearly states that children/adults were recruited consecutively or randomly. Case–control or two-gate studies should be answered no.

Was a case–control design avoided?
There is increased bias in a case–control (two-gate) study compared with a cohort (one-gate) study.

Were selection criteria clearly described (age limits and Centor/FeverPAIN scores)?
All inclusion criteria should be clearly specified. Lack of clear selection criteria, or different selection criteria, introduces bias through unclear adherence to consecutive or random sampling, and because there is a recognised bias with the reference standard detecting strep A carriage (rather than strep A detection), which is exacerbated if a greater proportion of less symptomatic patients are introduced.

Did the study avoid inappropriate exclusions?
Patients who meet the inclusion criteria should be given the index test. If > 5% meet the inclusion criteria but are not given the test, this is an inappropriate exclusion. If < 5% and no reasons are provided, this is also an inappropriate exclusion.

All patients who received the index test should have their results reported. If > 5% are not reported, this is an inappropriate exclusion. If < 5% are reported but no reasons are provided, this is also an inappropriate exclusion.

We would expect the whole cohort to receive a rapid test(s) (from one of our included list: Clearview Exact, BD Veritor Plus, Strep A Rapid Test, NADAL Strep A, OSOM Strep A test, QuikRead Go Strep A test kit, Alere TestPack +Plus Strep A, bioNexia Strep A, Biosynex, Sofia Strep A FIA) or a molecular test (from one of our included list: Alere i, cobas Liat Strep A Assay or Xpert Xpress Strep A). Also a comparator [Centor (modified Centor or McIsaac) or FeverPAIN] where included in the study design and a biological culture as the reference standard. Very small numbers of exclusions (< 5%) may be acceptable, if accompanied by reasonable explanations.

Were patients seen in an ambulatory care setting?
Patients seen as inpatients may vary in severity and have comorbidities affecting their diagnosis.

B. Concerns regarding applicability

Guidance
Patients aged < 5 years do not meet our inclusion criteria. If more than 10% of the sample are under 5 years this should be rated as high.

In the UK the test would be given following an assessment using Centor or FeverPAIN. The rapid test would be given only in people with Centor scores of > 2 points and FeverPAIN scores of > 1 point. If the study does not mention these tests or no assessment test was undertaken, it should be rated high concern. If the study included people with scores of ≤ 2 points on Centor or 1 point on FeverPAIN, this can only be classed as low risk of bias if the test accuracy is reported separately for Centor scores of > 2 points and FeverPAIN scores of > 1 point. If the test accuracy for low- and high-rated Centor/FeverPAIN groups are ONLY reported together, this should be reported as a high concern for applicability.

Domain 2: index test

The main sources of bias introduced by conducting and interpreting the index test are blinding and defining the threshold. If the reference standard is carried out before the index test (e.g. in case control studies) it is important to blind personnel to the results of the reference standard.

The QUADAS-2 tool requires a threshold to be prespecified in the methods to avoid adjustment of the threshold according to the test outcome. In manufactured tests the threshold has been predetermined. There is some subjectivity in how the RADT tests are read. If the operator claimed to follow the product insert then the subjectivity has been reduced; however, a bias still exists. There is no subjectivity in the molecular tests, which tell you on the screen whether or not strep A is present. In studies of test development, the threshold must be reported and must be prespecified.

A. Risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?
In cohort designs where the reference standard was given after or at the same time as the index test, answer yes. This is because the reference standard is read after a longer time period than the rapid test. If timing is unclear or the study has a case–control design then this is a yes only if blinding is specifically mentioned or if the index test is fully automated with no human interpretation.

Was a separate swab undertaken for the index test?
Manufacturers' specifications require separate swabs be taken for the index and reference standard. Using one swab for multiple purposes may reduce the amount of the sample and affect the accuracy of the test.

Was a threshold explicitly prespecified?
All manufactured rapid tests and have an inbuilt threshold; therefore, the answer should be low. If the threshold is not prespecified then it must be rated as high risk of bias. In test development studies it must explicitly state that the threshold has been prespecified and what the threshold is.

Is the test reading objective?

Molecular tests provide the result on the screen so should always be answered yes (low risk of bias). All rapid tests are subjectively read based on the internal inbuilt threshold bar the BD Veritor plus system, NADAL Strep A scan test, QuikRead Go Strep A test and Sofia Strep A FIA, which use analysers/readers to digitally display results. Any test where a subjective reading is taken will have a high risk of bias and should be answered no.

B. Concerns about applicability

If the study does not specify that the test was carried out to the manufacturer's specification the rating should be noted as unclear. Previous versions of included tests should be rated as high.

Domain 3: reference standard

The reference standard should be throat culture. FeverPAIN or Centor are appropriate comparator screening tests but not a reference standard.

The reference standard should be undertaken using *Staphylococcus* or *Streptococcus* agar or simple blood agar. Cultures using a blood agar should be incubated in an anaerobic atmosphere at 35–37 °C for 18–24 hours, with cultures read after > 18 hours. Alternatively, blood agar could be incubated in 5–10% CO_2 at 35–37 °C for 18–24 hours. Cultures using staphylococcal or streptococcal selective agar should be incubated at 35–37 °C in aerobic conditions for 18–48 hours and read after > 24 hours. Current guidance advises to re-examine plates at 48 hours that yield negative results at 24 hours.[29] If the culture is not incubated in the correct manner then there will be a high risk of bias.

Investigators will not be blinded to the clinical scoring tool but should be blinded to the reference standard.

A. Risk of bias

Was a separate swab taken for throat culture testing?

The American Academy of Pediatrics recommends separate swabs be taken for the index and reference standard testing (Mitul Patel, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK, personal communication). Using one swab for multiple purposes may reduce the amount of the sample and affect the accuracy of the test.

Is the reference standard likely to correctly classify the target condition?

If the reference standard used was throat culture and this was done appropriately then the answer should be yes. This should be a laboratory culture on a staphylococcal, streptococcal or blood agar plate during 48 hours. Were the culture medium, atmosphere, duration of incubation and GAS-confirmation technique described?

Were the reference standard results interpreted without knowledge of the results of the index test?

This can be rated as low providing the operator in the laboratory is competency assessed and follows the standard operating procedure. This is applicable to all types of laboratory cultures.

B. Concerns about applicability

The concern of applicability of the reference standard will be 'high' if any measure other than a throat culture is used. The culture should be carried out using a staphylococcal or streptococcal or simple blood agar plate, incubated as described above and then serotyped. If any of these measures differ then there is a high risk of bias. If it is not reported then this should be noted as unclear.

Domain 4: flow and timing

The index test should be carried out prior to the reference standard and to antibiotic prescribing.

A. Risk of bias

Was there an appropriate interval between index test(s) and reference standard?
The swab for throat culture should be taken at the same time as the swab for the RADT and should be processed within 48 hours. Consider the following:

- Were both index test(s) and reference standard (and comparator where included) all carried out at the same appointment?
- Were all swabs processed within 48 hours?

If the answer to any of these is no then this is high risk of bias.

Were both index test(s) and reference standard (and comparator where included) all carried out prior to commencement of antibiotics?
Patients should not have been treated with antibiotics prior to receiving the index test(s) and/or reference standard.

Did all patients receive a reference standard?
All should receive both the index test and reference standard. Very small numbers of exclusions (< 5%) may be acceptable, if accompanied by reasonable explanations.

Did all patients receive the same reference standard?
This question should be answered with 'no' if patients received different reference standards or if positive cases on the index test received a different reference standard to negative subjects.

Were all patients included in the analysis?
All patients should be included in the analysis. If inconclusive or intermediate results are not considered in the analysis the question should be answered with 'no'. Very small numbers of exclusions (< 5%) may be acceptable, if accompanied by reasonable explanations. If patients lost to follow-up were not included in the analysis or > 5% of patients were lost to follow-up (even if considered in the analysis) the question should be answered with 'no'. (The actual proportion of patients lost to follow-up needs to be recorded for each study.) In both cases the risk of bias should be classed as 'high'.

QUADAS-2 (unadjusted)

First author surname and year of publication:

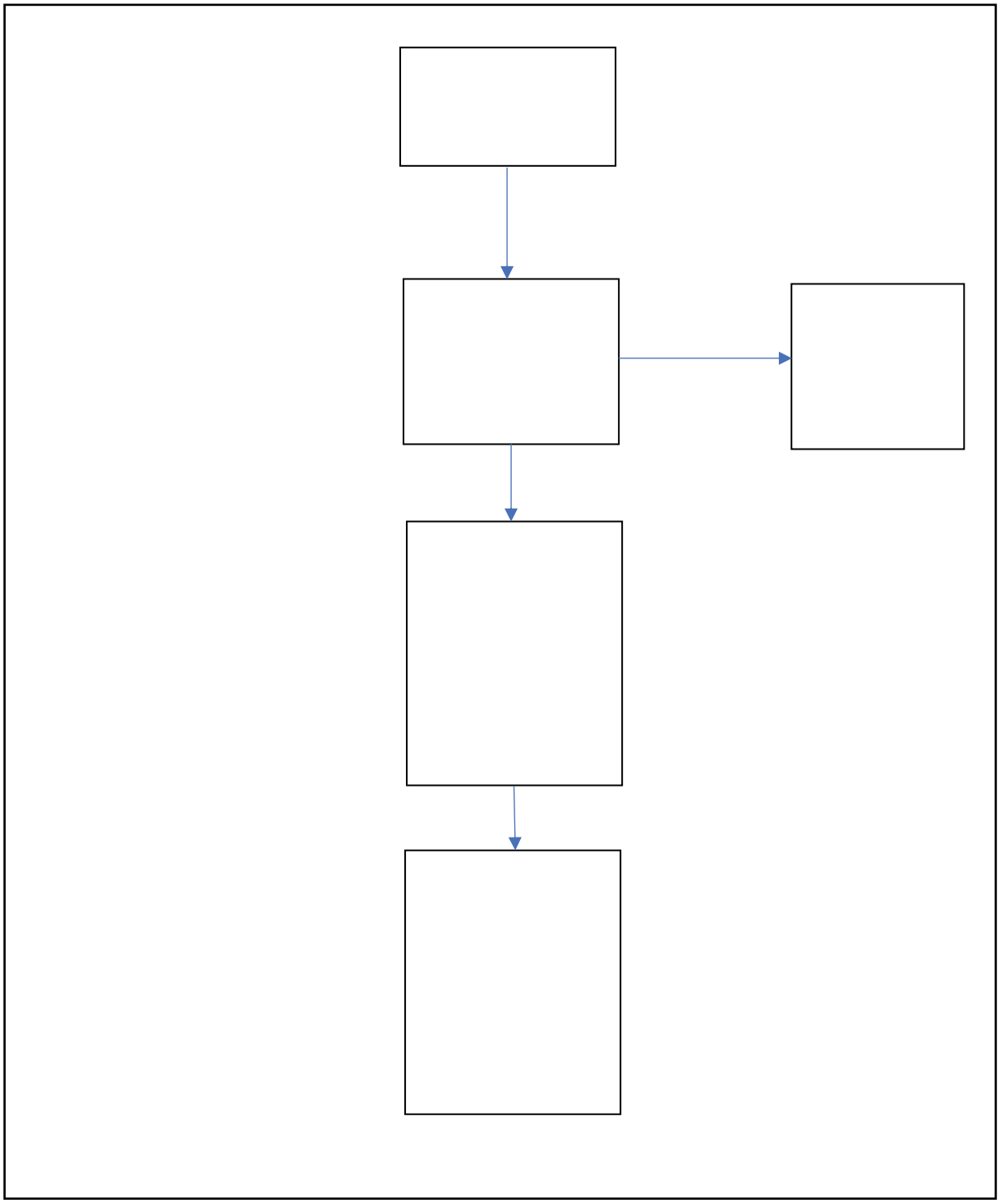
Name of first reviewer: HF *Name of second reviewer:*

Phase 1: State the review question:

Rapid Tests for Group A Streptococcal infections in people with a sore throat

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Comparator(s):
Reference standard and target condition: Culture. Strep A

Phase 2: Draw a flow diagram for the primary study



Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection:	
+ Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear
+ Was a case-control design avoided?	Yes/No/Unclear
+ Were selection criteria clearly described?	Yes/No/Unclear
+ Did the study avoid inappropriate exclusions?	Yes/No/Unclear
+ Were patients seen in ambulatory care setting?	Yes/No/Unclear
Could the selection of patients have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting)**:**	
Is there concern that the included patients do not match the review question?	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 2: INDEX TEST(S) **If more than one index test was used, please complete for each test.** **A. Risk of Bias**	
Describe the index test and how it was conducted and interpreted:	
+ Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/No/Unclear
+ Was a separate swab undertaken for the index test?	Yes/No/Unclear
+ If a threshold was used, was it pre-specified?	Yes/No/Unclear
+ Is the test reading objective?	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted:	
+ Was a separate swab taken for throat culture testing?	Yes/No/Unclear
+ Is the reference standard likely to correctly classify the target condition?	Yes/No/Unclear
+ Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 4: FLOW AND TIMING **A. Risk of Bias**	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):	
Describe the time interval and any intervention between index tests(s) and reference standard:	
+ Was there an appropriate interval (same appointment) between index test(s) and reference standard?	Yes/No/Unclear
+ Did all patients receive a reference standard?	Yes/No/Unclear
+ Did all patients receive the same reference standard?	Yes/No/Unclear
+ Were both index test(s) and reference standard (and comparator where included) all carried out prior to the commencement of antibiotics?	Yes/No/Unclear
+ Were all patients included in the analysis?	Yes/No/Unclear
Could the patient flow have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**

Appendix 5 Antibiotic-prescribing behaviours

TABLE 37 Randomised controlled trials on antibiotic-prescribing behaviours

Study (first author and year of publication)	Country	Index test	Study details	Antibiotic-prescribing behaviour
Little 2013[6]	UK	Alere TestPack Plus (IMI TestPack)	Three-armed trial with a delayed antibiotics arm (clinical assessment without a tool), a clinical tool arm and a rapid test following clinical tool arm. Clinicians given guidance to follow on prescribing Arm 1: delayed antibiotics control arm – depending on severity of presentation patients were given antibiotics, given no antibiotics or given a delayed prescription to collect after 3–5 days if symptoms did not improve or worsened Arm 2: clinical score arm – patients assessed using FeverPAIN. Patients with scores of 0 or 1 were not offered antibiotics. Immediate antibiotics were offered for patients with scores of ≥ 4 and for scores of 2 or 3 delayed antibiotics were offered Arm 3: RADT arm – those patients with a clinical score of 0 or 1 were not offered antibiotics or a RADT, those with a score of 2 were offered delayed antibiotics and those with scores of ≥ 3 were given a RADT. All those with negative RADTs were not offered antibiotics	Antibiotics offered immediately or a delayed prescription to 89% (185/207) in delayed prescription control arm, to 59% (124/211) in the clinical score arm and 40% (86/213) in the clinical score plus RADT arm Use of antibiotics ascertained from the patients with incomplete responses as follows: 46% (75/164) used antibiotics in the delayed prescription arm compared with 37% (60/161) in the clinical score arm and 35% (58/164) in the clinical score plus RADT arm
Llor 2011[45]	Spain	OSOM Strep A test	Two-arm cluster randomised trial. Health-care centres randomised to intervention (RADT) arm or control arm (management with clinical criteria only)	Control arm GPs prescribed antibiotics in 64% (168/262) of patients compared with 44% (123/281) in the RADT arm. Of the 60 test-positive cases, 59 were given antibiotics (98%). In those for whom the test was negative, 69/225 were given antibiotics (31%) Across both trial arms, antibiotic treatment was 'inappropriate' (as culture was negative) in 40% (210/526) of patients, and in 3% (16/526) of patients antibiotics were not prescribed when culture was positive; 153 of these cases

continued

TABLE 37 Randomised controlled trials on antibiotic-prescribing behaviours (*continued*)

Study (first author and year of publication)	Country	Index test	Study details	Antibiotic-prescribing behaviour
				were in the control arm and 73 were in the RADT arm. Category of inappropriate decision (overprescribing or underprescribing) is not reported by trial arm
Worrall 2007[55]	Canada	Clearview Exact Strep A	Four-armed trial: control arm using clinician's independent decisions as usual practice, arm using STDR (≤ 1, no need for antibiotics; 2, decisions made by the clinician; 3 or 4, antibiotics needed), arm using a rapid test (RADT) and arm using both STDR and RADT (≤ 1, no need for antibiotics; 2, RADT; 3 or 4, antibiotics needed). Clinicians were recommended to follow the guidance but it was not enforced	46.7% (247/533) of patients received antibiotics. 58% (82/141) usual practice, 55% (94/170) with Centor score alone compared with 27% (32/120) with rapid antigen testing alone and 38% (39/102) with combined rapid antigen testing and Centor score

TABLE 38 Before-and-after study on antibiotic-prescribing behaviours

Study (first author and year of publication)	Country	Index test	Study details	Antibiotic-prescribing behaviour
Bird 2018[35]	UK	bioNexia Strep A	Prospective cohort before-and-after study. Baseline antibiotic-prescribing data were collected retrospectively from October to November 2014 (method of diagnosis in this phase is not reported) and compared (following introduction of a new algorithm, RADT for those with a McIsaac score of > 3) with rates in August to November 2015 and September to November 2016. Only positive RADT given antibiotics but clinicians could prescribe if they still had a high level of clinical suspicion of strep A pharyngitis	Following implementation of an algorithm combining McIsaac scores and bioNexia Strep A Rapid Testing, antibiotic-prescribing rates fell steeply from 79% (166/210) at baseline to 24% (51/214) in year 1 and 28.2% (51/181) for the second year

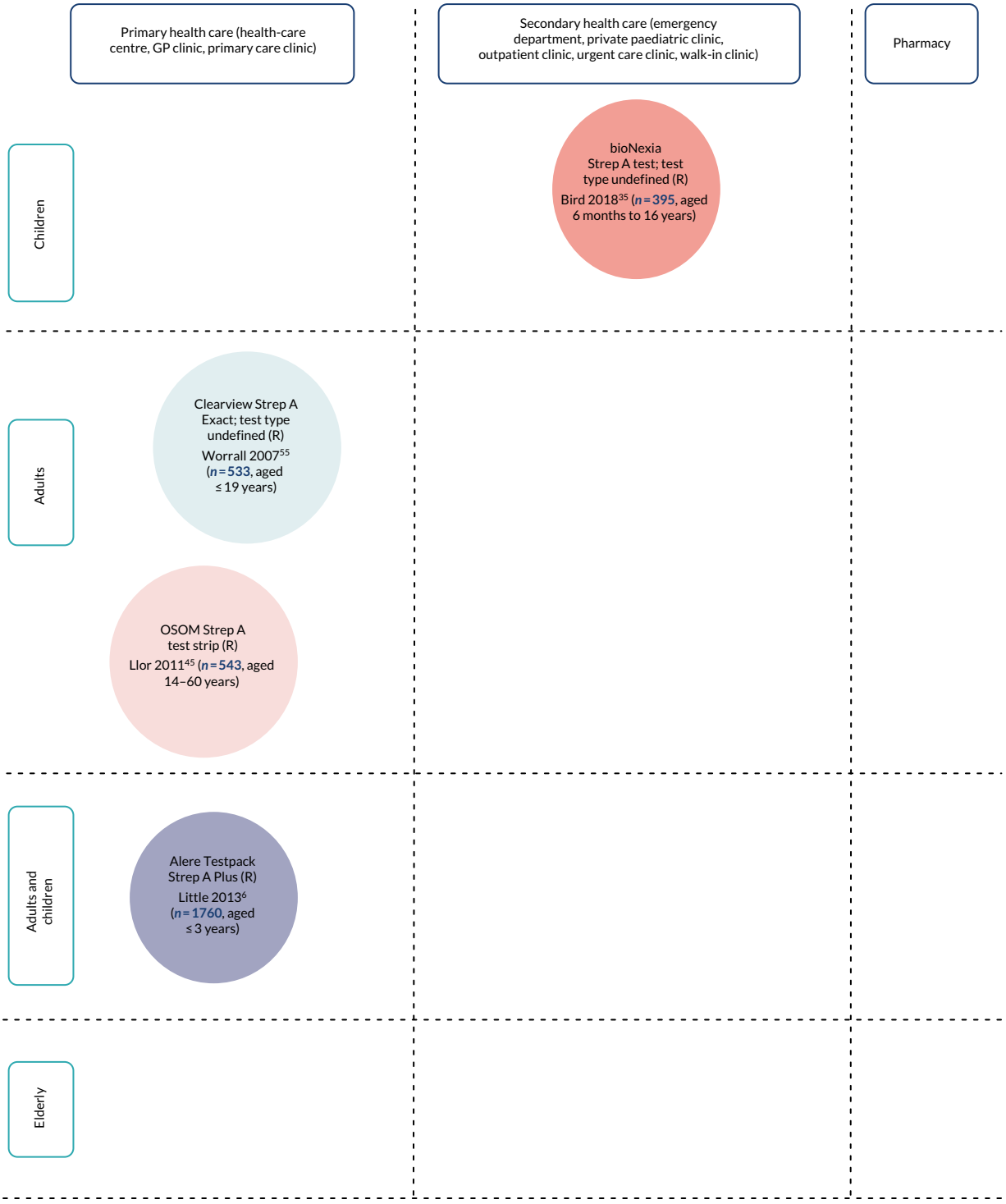


FIGURE 15 Diagram of studies with comparative data (RCTs and before-and-after studies) on antibiotic-prescribing rates by test type, setting and population. Note: lines between tests indicate head-to-head (direct) comparisons (none were found). M, molecular test; R, rapid test.

Appendix 6 Record of searches: cost-effectiveness

Sore throat/group A *Streptococcus* with economic evaluations/ quality of life/cost and resource use

Bibliographic databases

Summary of bibliographic database searches

Database	Date of search	Number of records from targeted search results (to screen first) + other results picked up by broader search = total number of records (+ update search results)
MEDLINE (via OvidSP)	22 January 2019 (updated 13 March 2019)	304 + 1728 = 2032 (+ 36)
EMBASE (via OvidSP)	22 January 2019 (updated 13 March 2019)	434 + 2673 = 3107 (+ 67)
NHS EED and HTA database (via CRD)	22 January 2019 (not updated as no new records added)	13 + 42 = 55
Science Citation Index and Conference Proceedings Citation Index – Science (via the Web of Science)	29 January 2019 (updated 13 March 2019)	260 + 1397 = 1657 (+ 17)
Cost-Effectiveness Analysis (CEA) Registry	29 January 2019 (updated 13 March 2019)	3 (+ 0)
EconPapers (RePEc)	29 January 2019 (updated 13 March 2019)	6 (+ 0)
ScHARRHUD	29 January 2019 (updated 13 March 2019)	0 (+ 0)

Total number of records from database searches: (1011 + 5849 = 6860) + 120 from 2019 update search = 6980.

Total number of records after deduplication: (522 + 2175 = 2697) + 58 from 2019 update search = 2755.

MEDLINE (via OvidSP)

Databases: Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions.

Date searched: 22 January 2019 (updated on 13 March 2019; see at the end of this search record).

Date range searched: 1946 to 21 January 2019.

Original search: 22 January 2019

1. exp Pharyngitis/ (15,095)
2. pharyngit*.ti,ab,kf. (5487)
3. (nasophyryngit* or rhinopharyngit* or epipharyngit*).ti,ab,kf. (178)
4. (tonsillit* or tonsilit*).ti,ab,kf. (5615)

5. ((sore or pain* or ache* or aching or inflam* or infect*) adj3 (pharyn* or throat* or tonsil* or nasopharyn* or rhinopharyn* or epipharyn*)).ti,ab,kf. (9975)
6. or/1-5 (25,268)
7. Streptococcal Infections/di, mi (13,421)
8. Streptococcus pyogenes/im, ip (5463)
9. 7 or 8 (16,691)
10. ((strep or streptococcal or group) adj2 A).ti,ab,kf. (564,113)
11. 9 and 10 (4859)
12. (strep* adj5 (throat* or pharyn* or tonsil*)).ti,ab,kf. (3410)
13. streptoco* A.ti,ab,kf. (480)
14. (group A adj5 streptoco*).ti,ab,kf. (9515)
15. ((streptococcus or strep or staphylococcus) adj1 (pyogenes or pyogenic)).ti,ab,kf. (7726)
16. ((streptococcus or strep) adj1 (epidemicus or erysipelatis or erysipelatos or hemolyticus or haemolyticus or scarlatinae or lancefield)).ti,ab,kf. (240)
17. (s pyogenes or pyogenes s or micrococcus scarlatinae).ti,ab,kf. (2497)
18. lancefield group.ti,ab,kf. (476)
19. gabhs.ti,ab,kf. (394)
20. or/11-19 (18,885)
21. exp Economics/ (571,394)
22. exp “Costs and Cost Analysis"/ (221,362)
23. Health Status/ (75,366)
24. exp “Quality of Life"/ (171,033)
25. exp Quality-Adjusted Life Years/ (10,672)
26. (pharmacoeconomic* or pharmaco-economic* or economic* or cost* or price or prices or pricing).ti,ab,kf. (752,907)
27. (expenditure$ not energy).ti,ab,kf. (27,109)
28. (value adj1 money).ti,ab,kf. (32)
29. budget*.ti,ab,kf. (26,932)
30. (health state* or health status).ti,ab,kf. (57,854)
31. (qaly* or ICER or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form 36 or shortform 36 or SF-36 or SF36 or SF-6D or SF6D or SF-12 or SF12 or health utilities index or HUI).ti,ab,kf. (224,115)
32. (markov or time trade off or TTO or standard gamble or SG or hrql or hrqol or disabilit* or disutilit* or net benefit or contingent valuation).ti,ab,kf. (215,735)
33. (quality adj2 life).ti,ab,kf. (248,124)
34. (decision adj2 model).ti,ab,kf. (6096)
35. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).ti,ab,kf. (54,743)
36. resource*.ti,ab,kf. (294,615)
37. (well-being or wellbeing).ti,ab,kf. (77,269)
38. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (2,072,673)
39. 6 and 38 (1622)
40. 20 and 38 (714)
41. 39 and 40 (304)
42. 39 or 40 (2032
43. 42 not 41 (1728)

Updated search: 13 March 2019

Re-ran above search with following date limits:

44. limit 42 to ed=20190122-20190313 (8)
45. limit 42 to ep=20190122-20190313 (17)

46. 2019*.dt,ez. (265,815)
47. 42 and 46 (29)
48. 44 or 45 or 47 (36)

Total after removing duplicates with previous search: 27.

EMBASE (via OvidSP)

Databases: EMBASE Classic and EMBASE.

Date range searched: 1947 to 2019 week 3.

Date searched: 22 January 2019 (updated on 13 March 2019; see at the end of this search record).

Original search: 22 January 2019

1. *streptococcal pharyngitis/ or *pharyngitis/ or *rhinopharyngitis/ or *sore throat/ or *tonsillitis/ or *chronic tonsillitis/ or *palatine tonsillitis/ (12,255)
2. pharyngit*.ti,ab,kw. (7907)
3. (nasophyryngit* or rhinopharyngit* or epipharyngit*).ti,ab,kw. (381)
4. (tonsillit* or tonsilit*).ti,ab,kw. (8351)
5. ((sore or pain* or ache* or aching or inflam* or infect*) adj3 (pharyn* or throat* or tonsil* or nasopharyn* or rhinopharyn* or epipharyn*)).ti,ab,kw. (15,999)
6. or/1-5 (32,848)
7. Streptococcus infection/di (3828)
8. Streptococcus pyogenes/ or streptococcus group a/ or group A streptococcal infection/ (24,060)
9. 7 or 8 (27,010)
10. ((strep or streptococcal or group) adj2 A).ti,ab,kw. (799,616)
11. 9 and 10 (9653)
12. (strep* adj5 (throat* or pharyn* or tonsil*)).ti,ab,kw. (4855)
13. streptoco* A.ti,ab,kw. (636)
14. (group A adj5 streptoco*).ti,ab,kw. (12,259)
15. ((streptococcus or strep or staphylococcus) adj1 (pyogenes or pyogenic)).ti,ab,kw. (9749)
16. ((streptococcus or strep) adj1 (epidemicus or erysipelatis or erysipelatos or hemolyticus or haemolyticus or scarlatinae or lancefield)).ti,ab,kw. (391)
17. (s pyogenes or pyogenes s or micrococcus scarlatinae).ti,ab,kw. (3246)
18. lancefield group.ti,ab,kw. (566)
19. gabhs.ti,ab,kw. (507)
20. or/11-19 (24,568)
21. exp health economics/ (803,214)
22. exp health status/ (219,256)
23. exp "quality of life"/ (447,670)
24. exp quality adjusted life year/ (23,005)
25. (pharmacoeconomic* or pharmaco-economic* or economic* or cost* or price or prices or pricing).ti,ab,kw. (986,866)
26. (expenditure* not energy).ti,ab,kw. (37,545)
27. (value adj2 money).ti,ab,kw. (2246)
28. budget*.ti,ab,kw. (35,940)
29. (health state* or health status).tw. (75,069)
30. (qaly* or ICER or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form 36 or shortform 36 or SF-36 or SF36 or SF-6D or SF6D or SF-12 or SF12 or health utilities index or HUI).ti,ab,kw. (321,459)
31. (markov or time trade off or TTO or standard gamble or SG or hrql or hrqol or disabilit* or disutilit* or net benefit or contingent valuation).ti,ab,kw. (311,593)

32. (quality adj2 life).tw. (384,281)
33. (decision adj2 model).tw. (9229)
34. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw. (78,125)
35. resource*.ti,ab,kw. (375,642)
36. (well-being or wellbeing).tw. (99,946)
37. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (2,880,444)
38. 6 and 37 (2459)
39. 20 and 37 (1082)
40. 38 and 39 (434)
41. 38 or 39 (3107)
42. 41 not 40 (2673)

Updated search: 13 March 2019

Re-ran the above search with the following date limits:

43. limit 41 to dd=20190122-20190313 (16)
44. limit 41 to em=201901-201903 (25)
45. 43 or 44 (41)
46. limit 41 to dc=20190122-20190313 (42)
47. 45 or 46 (67)

Total after removing duplicates with other update and previous searches: 25.

NHS Economic Evaluation Database and Health Technology Assessment database (via Centre for Reviews and Dissemination)

Searched on 22 January 2019. (Not updated because no new records have been added to NHS EED since 31 March 2015 or to the HTA database since 31 March 2018. The INAHTA website was checked in March 2019 to see if a new platform for the HTA database was available.)

Original search: 22 January 2019

1. MeSH DESCRIPTOR Pharyngitis EXPLODE ALL TREES IN DARE,NHSEED,HTA (73)
2. (pharyngit*) (85)
3. (nasophyryngit*) OR (rhinopharyngit*) OR (epipharyngit*) (5)
4. (tonsillit* or tonsilit*) (43)
5. (((sore or pain* or ache* or aching or inflam* or infect*) adj3 (pharyn* or throat* or tonsil* or nasopharyn* or rhinopharyn* or epipharyn*))) (91)
6. #1 OR #2 OR #3 OR #4 OR #5 (163)
7. MeSH DESCRIPTOR Streptococcal Infections WITH QUALIFIERS DI, MI IN DARE, NHSEED,HTA (31)
8. MeSH DESCRIPTOR Streptococcus pyogenes WITH QUALIFIERS IM, IP IN DARE, NHSEED,HTA (13)
9. #7 OR #8 (36)
10. (((strep or streptococcal or group) adj2 A)) (2025)
11. #9 AND #10 (17)
12. ((strep* adj5 (throat* or pharyn* or tonsil*))) (39)
13. (streptoco* adj1 A) (10)
14. ((group A adj5 streptoco*)) (27)
15. (((streptococcus or strep or staphylococcus) adj1 (pyogenes or pyogenic))) (25)
16. (((streptococcus or strep) adj1 (epidemicus or erysipelatis or erysipelatos or hemolyticus or haemolyticus or scarlatinae or lancefield))) (0)

17. ((s pyogenes or pyogenes s or micrococcus scarlatinae)) (1)
18. (lancefield group) (0)
19. (gabhs) (8)
20. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 (51)
21. #6 AND #20 (43)
22. (#21) IN NHSEED, HTA (13)
23. #6 OR #20 (171)
24. (#23) IN NHSEED, HTA (55)
25. (#24 NOT #22) IN NHSEED, HTA (42)

Science Citation Index and Conference Proceedings Citation Index – Science (via the Web of Science)

Date of search: 29 January 2019 (updated on 13 March 2019; see at the end of this search record).

Original search: 29 January 2019

Note: search record reads from bottom to top.

# 20	1397	#19 not #18 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 19	1657	#17 OR #16 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 18	260	#17 AND #16 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 17	709	#15 AND #14 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 16	1208	#15 AND #5 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 15	3,164,661	TS=("quality of life" or qol or hrql or hrqol or ("quality adjusted life" NEAR/0 year*) or qaly* or icer or cost* or economic* or pharmacoeconomic* or pharmaco-economic* or price or prices or pricing or (expenditure* not energy) or (value NEAR/1 money) or budget* or euro-qol or utilit* or disutilit* or (net NEAR/0 benefit*) or (contingent NEAR/0 valuation*) or euroqol or "euro qol" or eq5d or eq-5d or "short-form 36" or "shortform 36" or sf-36 or sf36 or sf-6d or sf6d or sf-12 or sf12 or "health utilities index" or hui or (time NEAR/0 trade*) or tto or "standard gamble" or sg or markov or (decision NEAR/1 model*) or (visual NEAR/0 analog*) or "discrete choice" or ((health* NEAR/0 year*) NEAR/0 equivalen*) or (health NEAR/0 stat*) or (willing* NEAR/1 pay) or resource* or wellbeing or well-being) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 14	17,381	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 13	308	TS=gabhs *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 12	445	TS="lancefield group" *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 11	2059	TS=("s pyogenes" OR "pyogenes s" OR "micrococcus scarlatinae") *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*

# 10	60	TS=((strep*) NEAR/0 (epidemicus OR erysipelatis OR erysipelatos OR hemolyticus OR haemolyticus OR scarlatinae OR lancefield)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 9	7163	TS=((strep*) NEAR/0 (pyogenes OR pyogenic)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 8	9682	TS=("group A" NEAR/4 strep*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 7	1165	TS="strep* A" *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 6	2877	TS=(strep* NEAR/4 (throat* OR pharyn* OR tonsil*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 5	12,508	#1 OR #2 OR #3 OR #4 *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 4	7034	TS=((sore OR pain* OR ache* OR aching OR inflam* OR infect*) NEAR/2 (pharyn* OR throat* OR tonsil* OR nasopharyn* OR rhinopharyn* OR epipharyn*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 3	2716	TS=(tonsillit* OR tonsilit*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 2	96	TS=(nasophyryngit* OR rhinopharyngit* OR epipharyngit*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*
# 1	4667	TS=pharyngit* *Indexes=SCI-EXPANDED, CPCI-S Timespan=1900-2019*

Updated search: 13 March 2019

Re-ran the above search with the following date limits.

# 19	17	#17 or #16 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2019-2019*

Total after removing duplicates with other update and previous searches: 6.

Cost-Effectiveness Analysis (CEA) Registry

Searched on 29 January 2019 (updated on 13 March 2019; see at the end of this search record).

Original search: 29 January 2019

Single-term searches, deduplicated and screened online. Results (number selected):

pharyngitis	6 (3)
pharynx	4 (0)
nasopharyngitis	0 (0)
nasopharynx	0 (0)
rhinopharyngitis	0 (0)
rhinopharynx	0 (0)
epipharyngitis	0 (0)

epipharynx	0 (0)
tonsillitis	0 (0)
tonsilitis	0 (0)
tonsil	3 (1, already got from search on pharyngitis above)
throat	6 (2, both already got from search on pharyngitis above)
streptococcus	22 (2, both already got from search on pharyngitis above)
streptococcal	7 (2, both already got from search on pharyngitis above)
strep	30 (3, both already got from search on pharyngitis above)

Potentially relevant results downloaded to EndNote: 3.

Updated search: 13 March 2019
Re-ran the above searches on 13 March 2019. No further records added.

EconPapers (RePEc)
Date searched: 30 January 2019 (updated on 13 March 2019; see at the end of this search record).

Original search: 30 January 2019; advanced search
#1

((pharyn* | nasopharyn* | rhinopharyn* | epipharyn* | tonsil* | throat) + (strep* | "lancefield group" | pyogenes | micrococcus)) 6

#2

((sore | pain* | ache* | aching | inflam* | infect*) + (throat | pharyn* | tonsil* | nasopharyn* | rhinopharyn* | epipharyn*)) 31

#3

pharyngitis | nasopharyngitis | rhinopharyngitis | epipharyngitis | tonsilitis | tonsillitis 28

Above three searches combined with OR (|):

#4

((pharyn* | nasopharyn* | rhinopharyn* | epipharyn* | tonsil* | throat) + (strep* | "lancefield group" | pyogenes | micrococcus)) | ((sore | pain* | ache* | aching | inflam* | infect*) + (throat | pharyn* | tonsil* | nasopharyn* | rhinopharyn* | epipharyn*)) | (pharyngitis | nasopharyngitis | rhinopharyngitis | epipharyngitis | tonsilitis | tonsillitis) 52

Deduplicated and screened online, selecting all potentially relevant.

Potentially relevant results downloaded to EndNote: 6.

Updated search: 13 March 2019
Re-ran above combination search on 13 March 2019. One further record added, but this was not relevant.

School of Health and Related Research Health Utilities Database

Searched on 30 January 2019 (updated on 13 March 2019; see at the end of this search record).

Original search: 30 January 2019

Single-term searches, deduplicated and screened online. Results (number selected):

pharynx*	0 (0)
nasopharyn*	0 (0)
rhinopharyn*	0 (0)
epipharyn*	0 (0)
tonsil*	0 (0)
throat*	1 (0)
strep*	0 (0)
gapbs	0 (0)
pyogene*	0 (0)

Potentially relevant results downloaded to EndNote: 0.

Updated search: 13 March 2019

Re-ran above searches on 13 March 2019. No further records added.

Other sources

In addition to these searches, any relevant cost-effectiveness studies identified during the clinical effectiveness review were brought to the attention of the reviewers.

Search engine

Google: searched 22 March 2019.

Search strategy

(HTA OR "health technology assessment") AND (pharyngitis OR strep OR streptococcus OR streptococcal).

Checked first 20 records.

Appendix 7 Excluded studies after full-text papers received for group A *Streptococcus* economics search

Study (first author and year of publication)	Title	Reason for exclusion
Banerjee 2018[104]	Rapid tests for the diagnosis of group A streptococcal infection: a review of diagnostic test accuracy, clinical utility, safety, and cost-effectiveness	The review provides information on two cost-effectiveness studies. One study has been included[76] and the other study was excluded as it is not an economic evaluation[a] and the test is outside the NICE scope[105]
Benjamin 2000[106]	The costs of testing for streptococcal pharyngitis in the office laboratory	Letter to editor commenting on Tsevat and Kotagal[107] Not an economic evaluation[a]
Boyler 2002[108]	A cost-effectiveness analysis of recommended strategies for acute pharyngitis	Abstract Test outside NICE scope
Ehrlich 2002[109]	Cost-effectiveness of treatment options for prevention of rheumatic heart disease from group A streptococcal pharyngitis in a pediatric population	No specific test stated
Giraldez-Garcia 2011[110]	Diagnosis and management of acute pharyngitis in a paediatric population: a cost-effectiveness analysis	No specific test stated
Klepser 2011[111]	Cost-effectiveness of pharmacist provided care for the treatment of adult pharyngitis	Abstract No specific test stated
Klepser 2012[80]	Cost-effectiveness of pharmacist provided care for the treatment of adult pharyngitis	No specific test stated
Komaroff 1983[112]	A cost-effectiveness analysis of alternate strategies for management of sore throat	Abstract No specific test stated
Lathia 2018[113]	Cost-minimization analysis of community pharmacy-based point-of-care testing for strep throat in 5 Canadian provinces	No specific test stated
Maizia 2012[114]	Diagnostic strategies for acute tonsillitis in France: a cost-effectiveness study	Not in English (in French) No specific test stated
Malecki 2017[115]	Rapid strip tests as a decision-making tool about antibiotic treatment in children – a prospective study	Not an economic evaluation[a] No comparator
Meier 1990[116]	Effects of a rapid antigen test for group A streptococcal pharyngitis on physician prescribing and antibiotic costs	No specific test stated
Mlejnek 2014[100]	Utility and cost effectiveness of throat culture in the treatment of patients with negative rapid strep screens	No specific test stated
Neuner 2003[78]	Diagnosis and management of adults with pharyngitis. A cost-effectiveness analysis	Test outside NICE scope

Study (first author and year of publication)	Title	Reason for exclusion
Polisena 2009[117]	Point of care testing for streptococcal sore throat: a review of diagnostic accuracy, cost-effectiveness, and guidelines	The review provides information on one cost-effectiveness study that was excluded as it did not mention a specific test[79]
Tsevat 1999[107]	Management of sore throats in children: a cost-effectiveness analysis	No specific test stated
Van Howe 2006[79]	Diagnosis and management of pharyngitis in a pediatric population based on cost-effectiveness and projected health outcomes	No specific test stated

a Not looking at incremental costs and incremental benefits.

Appendix 8 Data extraction for cost-effectiveness studies

TABLE 39 Data extraction for cost-effectiveness studies: Little *et al.*[76]

Study details subheading	Description of study details
Study details	
Study title	PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive RCT with nested qualitative study and cost-effectiveness study
First author	Paul Little (Programme Director of Programme Grants for Applied Research, Editor-in-Chief for the *Programme Grants for Applied Research* journal and member of the NIHR Journals Library Board)
Co-authors	Richard Hobbs, Michael Moore, David Mant, Ian Williamson, Cliodna McNulty, Gemma Lasseter, MY Edith Cheng, Geraldine Leydon, Lisa McDermott, David Turner, Rafael Pinedo-Villanueva, James Raftery [previously a member of the NIHR Journals Library Editorial Group (2012–14), current member of NIHR HTA and EME Editorial Board, previously Director of the Wessex Institute and Head of NIHR Evaluation, Trials and Studies Coordinating Centre], Paul Glasziou and Mark Mullee on behalf of the PRISM investigators
Source of publication	*Health Technology Assessment* 2014, Volume 18, Issue 6
Language	English language
Publication type	Original article
Inclusion criteria/study eligibility/PICOS	
Population (and subgroups)	Patients aged ≥ 3 years, who had acute sore throat
Intervention(s)	RADTs used with clinical score (FeverPAIN) All patients received the clinical scoring tool. Those with a score of 0 or 1 were not offered antibiotics or a RADT, those with a score of 2 were offered delayed antibiotics and those with scores of ≥ 3 were given a RADT. All those with negative RADTs were not offered antibiotics
Comparator(s)	Delayed antibiotics (control group) or clinical score only In the control group, depending on the severity of their presentation patients were given antibiotics, given no antibiotics or given a delayed prescription to collect after 3–5 days if symptoms did not improve or worsened In the clinical score group, patients were assessed using the FeverPAIN clinical scoring tool. Patients with scores of 0 or 1 were not offered antibiotics. Immediate antibiotics were offered to patients for scores of ≥ 4 and for scores of 2 or 3 delayed antibiotics were offered
Outcome(s)	Point change in symptom severity score (primary outcome measure in trial) and QALYs based on EQ-5D The symptom severity score is a two-item score (sore throat, difficulty swallowing); each symptom was scored 0 = no problem to 6 = as bad as it can be. A higher score indicates worse symptoms

continued

TABLE 39 Data extraction for cost-effectiveness studies: Little *et al.*[76] (*continued*)

Study details subheading	Description of study details
Study design	Economic analysis alongside a clinical trial
Setting and location	GP clinics in south and central England
Type of economic evaluation	Cost-effectiveness and cost–utility analysis
Methods	
Study perspective	NHS perspective
Time horizon	14 days and 28 days (1 month) after randomisation
Discount rate	Not applicable
Measurement of effectiveness	EQ-5D measure completed at baseline and 14 days after recruitment and recorded in a patient-completed diary
Measurement and valuation of preference-based outcomes	EQ-5D values were scored using the standard UK tariff
Resource use and costs	Resource use data were obtained from GP case notes and from study clinicians. Data included GP and nurse practitioner visits; antibiotics; practice visits for complications of infections and antibiotic complications; and hospital admissions related to infections. Costs included test costs, staff time, medications, complications and hospital admissions. Unit costs were obtained from the Unit Costs of Health and Social Care, NHS Reference Costs and NHS drug tariff The costs associated with the clinical score plus the test comprised the additional time required to provide the intervention as well as the cost of the RADT (£3.25 per test; £65 for 20 tests)
Currency, price date and conversion	Costs are in 2010/11 prices in Great British pounds
Model type	None, as it was based on trial data
Assumptions	EQ-5D results for the end of the 28-day follow-up period were not available; therefore, the values obtained at the end of the 14-day period were assumed to persist to the end of the study period; that is, the last value obtained was carried forward for 14 days
Analytical methods	Incremental costs and outcomes presented
Results	
Study parameters	Means and 95% CIs were generated for use cost variables. Mean values (with 95% CI) for outcome variables (both symptom score and QALYs) were estimated using regression equations controlling for baseline characteristics (fever and baseline symptoms)
Incremental costs and outcomes	Cost-effectiveness analysis • Mean cost in each group was £44 (clinical score; $n = 167$), £49 (RADT; $n = 163$) and £51 (delayed prescribing; $n = 168$) • Mean point estimate in severity score was 2.83 (clinical score), 2.84 (RADT) and 3.15 (delayed prescribing) • Overall results showed that the clinical score group dominated the other two groups, being more clinically effective (having a lower symptom score) and less costly Cost–utility analysis (complete-case analysis, $n = 257$) • Mean cost in each group was £46 (clinical score), £49 (RADT) and £50 (delayed prescribing) • Mean QALYs at 28 days were 0.0174 (clinical score), 0.0175 (RADT) and 0.0171 (delayed prescribing) • As the QALY gain is marginally higher in the test group than in the clinical score group, the RADT generates additional QALYs at £24,528 per QALY. Delayed prescribing was dominated

TABLE 39 Data extraction for cost-effectiveness studies: Little *et al.*[76] (*continued*)

Study details subheading	Description of study details
Characterising uncertainty	Bootstrapping using 5000 samples was used to generate CEACs. Bootstrapping was also used to generate scatterplots on the cost-effectiveness plane At a value of £30,000 per QALY, the probabilities that the three groups were cost-effective were 28%, 38% and 35%, for the delayed prescribing, clinical score and RADT groups, respectively, for the 28-day QALY gain
Discussion	
Study findings	The clinical scoring tool (FeverPAIN) was effective in helping to reduce symptoms, and the costs in all three groups were similar. The cost–utility analysis was less clear, as QALY differences were very small, generating wide CIs. The CEACs for the cost–utility study indicate that clinical score is most likely to be cost-effective over all values; however, they also indicate considerable uncertainty
Limitations	• 14-day diary had EQ-5D data for only two time points (0 and 14 days) • The smaller QALY data set may not be representative of the larger group of individuals in the cost-effectiveness study • Time frame was short; hence, longer-term impacts were not known
Generalisability	The generalisability of the analysis may be limited to the unit costs used in the analysis
Other	
Source of funding	The study was funded by the NIHR HTA programme
Conflicts of interest	None declared
Comments	None
Authors conclusion	
Using a clinical score appears to be an efficient use of health-care resources compared with either delayed antibiotic prescribing or the use of a RADT combined with a clinical score	
Reviewer's conclusion	
The authors used appropriate economic methods for the study	

EME, Efficacy and Mechanism Evaluation; NIHR, National Institute for Health Research; PICOS, participants, interventions, comparisons, outcomes and study design.
Note
Name of first reviewer: Hema Mistry. Name of second reviewer: Felix Achana.

Appendix 9 Adult primary care model: exploratory sensitivity analyses

Adult primary care model: prevalence of group A *Streptococcus* and clinical score threshold for starting antibiotics (usual-care arm) and testing (intervention arm)

In the base case, a cut-off score of 3 points on the Centor scale was used as the threshold for starting antibiotic treatment, with scores of ≥ 3 points indicating positive strep A infection. Changing this threshold to a score of ≥ 2 points had minimal impact on the base-case cost-effectiveness estimates. However, a threshold of ≥ 1 point for initiating point-of-care testing in primary care (equivalent to a test-all approach) favoured testing and changed the QALY difference from incremental QALY loss (–0.00396 per 1000 individuals) to incremental QALY gain (0.00346 per 1000 individuals) for Clearview Exact Strep A test cassette (Abbott Laboratories) and Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) compared with usual care (*Table 40*). The corresponding ICERs changed from these two tests being dominated in the base case to £7,071,480 and £6,875,048 per QALY gained for the cassette and dipstick versions, respectively, when compared with usual care.

The cost-effectiveness estimates were also sensitive to the prevalence of strep A among adults presenting in primary care. Increasing the prevalence rate from 22.6% (base-case model) to 35.9% (upper estimate from studies included in systematic review of test accuracy studies) generally favoured usual care (results not shown here); however, decreasing the prevalence to 10% (the value used in the Neuner *et al.* study[78]) favoured the intervention arm (i.e. testing). In the majority of cases, the ICERs did not change substantially to influence interpretation of cost-effectiveness, but the ICERs for Clearview Exact Strep A dipstick – test strip and Clearview Exact Strep A test – cassette (Abbott Laboratories) changed from being dominated (less effective and more costly) to being more effective and more costly at a 10% prevalence rate (see *Table 40*).

TABLE 40 Adult primary care model: deterministic sensitivity analyses – Centor threshold for starting antibiotic therapy and prevalence of strep A

	Base case			Sensitivity analysis		
Test	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 2 – changed Centor threshold for starting antibiotics from ≥ 3 to ≥ 1 points						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	–0.00396	Dominated	£24,462	0.00346	£7,071,480
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	–0.00396	Dominated	£23,783	0.00346	£6,875,048
Sensitivity analysis 5 – changed strep A prevalence from 22.6% (base case) to 10% (Neuner et al.[78])						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	–0.00396	Dominated	£6092	0.00131	£4,638,696
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	–0.00396	Dominated	£5923	0.00131	£4,510,168

Adult primary care model: complication rates in treated and untreated group A streptococcal infection

The ICERs for only Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A dipstick – cassette (Abbott Laboratories) were sensitive to modelled rates of complications (peritonsillar abscess, quinsy and cellulitis as the probabilities used in the model represented all of these complications as shown *Table 41*). In the base-case analysis, strep A-related complications rates were set to 1.5% for untreated infection and 1.3% for treated strep A infection based on UK primary care data published by Little *et al.*[86] Halving and doubling the complications rates in the untreated group did not influence ICERs substantially but doubling complications in the treated infection to 2.6% favoured testing. The ICER for the Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A cassette (Abbott Laboratories) changed from being dominated in the base case by usual care to £3,935,182 and £4,062,173 per QALY gained compared with usual care, respectively (see *Table 41*).

Adult primary care model: side effects of penicillin

Cost-effectiveness estimates were most sensitive to modelled rates of penicillin-induced anaphylaxis. In the base case, penicillin-induced anaphylaxis was set to 0.01% probability (see *Table 23*) and a utility decrement of 9 quality-adjusted life-days lost (see *Table 24*) based on figures reported in the Neuner *et al.* study,[78] with £1744 in treatment costs (Hex *et al.*[93]), reflecting the rare but serious nature of this event. Changing the rate of penicillin-induced anaphylaxis from 0.01% to 0.64% as reported in Van Howe and Kusnier[79] favoured testing: the ICER for Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A cassette (Abbott Laboratories) changed from being dominated by usual care in the base case to £3,935,182 and £4,062,173 per QALY gained compared with usual care. When the rate of mild penicillin rash was doubled from 2% to 4%, the ICER for Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A cassette (Abbott Laboratories) changed from being dominated by usual care in the base case to £288,702 and £299,305 per QALY gained compared with usual care, respectively (*Table 42*).

Adult primary care model: assume testing within standard general practice consultation time

The base-case analysis assumes that the typical general practice consultation duration of 9.22 minutes on average[90] is not sufficient to administer and process tests concurrently with usual consultation activities. Consequently, 5–12 minutes (depending on test) of additional clinician time was added when

TABLE 41 Adult primary care model: deterministic sensitivity analyses – complications following strep A infection

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 10 – doubled complications in treated strep A to 2.6%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	–0.00396	Dominated	£6399	0.00158	£4,062,173
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	–0.00396	Dominated	£6199	0.00158	£3,935,182

TABLE 42 Adult primary care model: deterministic sensitivity analyses – exploring the impact of complications of penicillin

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 16 – doubled rates of mild penicillin reaction (rash) to 4%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	−0.00396	Dominated	£6399	0.00107	£4,062,173
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	−0.00396	Dominated	£6199	0.00107	£3,935,182
Sensitivity analysis 17 – changed rates of anaphylaxis from 0.01% (Neuner et al.[78]) to 0.64% (Van Howe and Kusnier[79])						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	−0.00396	Dominated	£5647	0.01887	£299,305
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	−0.00396	Dominated	£5447	0.01887	£288,702

calculating test costs to account for longer consultation during testing in primary care. Excluding the additional cost of clinician time favoured testing but the ICERs for only the five NADAL tests fell below £100,000 per QALY gained compared with usual care (*Table 43*).

TABLE 43 Adult primary care model: deterministic sensitivity analyses – exploring the impact of excluding additional clinician time to administer and process test results

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 22 – assume testing within standard GP time						
NADAL Strep A – test strip (nal von minden GmbH)	£5248	0.00388	£1,353,677	£171	0.00388	£44,184
NADAL Strep A – cassette (nal von minden GmbH)	£5298	0.00388	£1,366,577	£221	0.00388	£57,085
NADAL Strep A plus – cassette (nal von minden GmbH)	£5323	0.00388	£1,373,029	£246	0.00388	£63,537
NADAL Strep A plus – test strip (nal von minden GmbH)	£5272	0.00388	£1,360,126	£196	0.00388	£50,636
NADAL Strep A scan test – cassette (nal von minden GmbH)	£5438	0.00388	£1,402,700	£361	0.00388	£93,211

Adult primary care model: utility decrement, group A *Streptococcus* sore throat and related complications

The base-case estimates were sensitive to changes in disutility associated with strep A sore throat and related complications. Decreasing the utility decrement associated with untreated strep A by half favoured testing, and doubling it favoured usual care (*Table 44*). All other testing scenarios involving doubling the utility decrements for treated strep A infection and penicillin-induced rash produced ICERs favourable to testing (key result changes are presented in *Table 44*).

TABLE 44 Adult primary care model: deterministic sensitivity analyses – utility decrement, strep A sore throat and related complications

	Base case			Sensitivity analysis		
Test	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 27 – halved the utility decrement, untreated strep A						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	−0.00396	Dominated	£7033	0.00667	£1,054,577
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	−0.00396	Dominated	£6833	0.00667	£1,024,581
Sensitivity analysis 28 – doubled utility decrement, untreated strep A						
Strep A Rapid Test – cassette (Biopanda Reagents)	£6295	0.00311	£2,026,496	£6295	−0.0002	Dominated
Strep A Rapid Test – test strip (Biopanda Reagents)	£6250	0.00311	£2,012,006	£6250	−0.0002	Dominated
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£5634	0.00293	£1,924,717	£5634	−0.0004	Dominated
Sensitivity analysis 30 – doubled utility decrement, treated strep A						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	−0.00396	Dominated	£7033	0.00879	£799,685
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	−0.00396	Dominated	£6833	0.00879	£776,939
Sensitivity analysis 36 – doubled utility decrement, penicillin-induced rash						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7033	−0.00396	Dominated	£7033	0.00107	£6,554,023
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£6833	−0.00396	Dominated	£6833	0.00107	£6,367,600

Appendix 10 Adult secondary care model: exploratory sensitivity analyses

Adults in secondary care: Centor threshold for starting antibiotics and testing

In the base-case secondary care model, a Centor score of ≥ 3 points was used as an indication for starting antibiotic treatment in the usual-care arm and to initiate testing using a point-of-care test in the intervention arm. Changing this threshold to a Centor score of ≥ 2 points favoured testing and produced ICERs for the NADAL's tests ranging between £30,230 and £69,690 per QALY gained compared with usual care (*Table 45*). Using a threshold of ≥ 1 point also favoured testing. The ICER for Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A cassette (Abbott Laboratories) changed from being dominated by usual care to £1,890,627 and £2,087,056 per QALY gained in comparison with usual care, respectively (see *Table 45*). The ICERs for NADAL's tests reduced further to between £22,220 and £56,190 per QALY gained in comparison with usual care. ICERs for the other tests remained well above £100,000 per QALY gained in these scenario analyses.

Adults in secondary care: prevalence of group A *Streptococcus*

Changing the prevalence of strep A infection in secondary care from 22.6% base-case value to 35.9% (upper value reported in studies included in the test accuracy systematic review) was less favourable to testing, with usual care dominating QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) in comparison with base-case results (*Table 46*). In contrast, a lower prevalence of disease was more favourable to testing, with ICERs for Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A cassette (Abbott Laboratories) changing from being dominated by usual care to £1,248,775 and £1,377,303 per QALY gained, respectively, in comparison with usual care (see *Table 46*). ICERs for NADAL's tests decreased to between £20,628 and £53,506 per QALY gained in comparison with usual care. ICERs for all other tests did not change substantially to suggest change in the direction of cost-effectiveness in comparison with usual care.

Adults in secondary care: complication rates

In the base-case analysis, strep A-related complications rates were set to 1.5% for untreated infection and 1.3% for treated infection based on UK primary care data published by Little *et al.*[86] Halving complications in the treated group to 0.65% and doubling the rate in the untreated group to 3% were less favourable to testing, with usual care dominating QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack +Plus Strep A – cassette (Abbott Laboratories). In contrast, doubling the complications rates in the treated group to 2.6% and halving the rate in the untreated group to 0.75% favoured testing. The ICER for the Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) and Clearview Exact Strep A cassette (Abbott) changed from being dominated by usual care in the base case to £712,813 and £839,805 per QALY gained, respectively (*Table 47*). ICERs for the NADAL tests ranged between £31,184 and £83,041 per QALY gained in the scenarios that favoured testing. ICERs for all other tests were much lower in comparison with the base-case estimates but still remained well above £100,000 per QALY gained in comparison with usual care.

TABLE 45 Adult secondary care model: deterministic sensitivity analyses – Centor threshold for starting antibiotics

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 1 – changed Centor threshold from ≥ 3 (base case) to ≥ 2 points						
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£307	0.01015	£30,230
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£412	0.01015	£40,614
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£465	0.01015	£45,807
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£359	0.01015	£35,422
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£707	0.01015	£69,690
Sensitivity analysis 2 – changed Centor threshold from ≥ 3 (base case) to ≥ 1 points						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	−0.00396	Dominated	£7220	0.00346	£2,087,056
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	−0.00396	Dominated	£6540	0.00346	£1,890,627
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£422	0.019	£22,220
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£592	0.019	£31,159
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£677	0.019	£35,629
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£507	0.019	£26,690
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£1068	0.019	£56,190

TABLE 46 Adult secondary care model: deterministic sensitivity analyses – prevalence of strep A

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 4 – changed strep A prevalence from 22.6% to 35.9%						
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£246	0.00282	£87,196
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£275	0.00282	£97,522
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£2120	−0.00241	Dominated
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£711	−0.00055	Dominated
Sensitivity analysis 5 – changed strep A prevalence from 22.6% to 10%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	−0.00396	Dominated	£1809	0.00131	£1,377,303
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	−0.00396	Dominated	£1640	0.00131	£1,248,775
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£101	0.00488	£20,628
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£143	0.00488	£29,280
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£164	0.00488	£33,606
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£122	0.00488	£24,954
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£261	0.00488	£53,506

TABLE 47 Adult secondary care model: deterministic sensitivity analyses – complications following strep A sore throat

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 9 – halved complications in treated infection to 0.65%						
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£191	0.0037	£51,597
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£241	0.0037	£65,100
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£266	0.0037	£71,853
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£216	0.0037	£58,350
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£2119	−0.00097	Dominated
Sensitivity analysis 10 – doubled complications in treated infection to 2.6%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	−0.00396	Dominated	£1323	0.00158	£839,805
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	−0.00396	Dominated	£1123	0.00158	£712,813
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£132	0.00422	£31,184
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£182	0.00422	£43,028
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£207	0.00422	£48,948
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£157	0.00422	£37,104
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£322	0.00422	£76,191
Sensitivity analysis 11 – halved complications in untreated infection to 0.75%						
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£148	0.00408	£36,415
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£198	0.00408	£48,684

TABLE 47 Adult secondary care model: deterministic sensitivity analyses – complications following strep A sore throat (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£223	0.00408	£54,820
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£173	0.00408	£42,551
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£338	0.00408	£83,041
Sensitivity analysis 12 – doubled complications in untreated infection to 3%						
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£217	0.00348	£62,404
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£267	0.00348	£76,786
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£292	0.00348	£83,978
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£242	0.00348	£69,596
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£2287	–0.00244	Dominated
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£795	–0.00031	Dominated

Adults in secondary care: adverse effects of penicillin

Cost-effectiveness estimates were most sensitive to the adverse effects of penicillin. Halving the mild/uncomplicated side effects of penicillin (rash) to 1.0% favoured usual care, and doubling it favoured testing (*Table 48*). The Clearview Exact Strep A cassette (Abbott Laboratories) and Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) are no longer dominated by usual care under this scenario. ICERs for the NADAL tests ranged between £8913 and £32,557 per QALY gained compared with usual care. In the base case, penicillin-induced anaphylaxis was set to 0.01% probability (see *Table 23*) and a utility decrement of 9 quality-adjusted life-days lost (see *Table 24*) based on figures reported in Neuner *et al.*,[78] with £1744 in treatment costs (Hex *et al.*[93]). Changing the rate of penicillin-induced rash from 0.01% to 0.64% as reported in Van Howe and Kusnier[79] favoured testing with Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) and all five NADAL tests, dominating usual care (see *Table 48*). ICERs for the remaining 12 tests ranged from £18 per QALY gained for Strep A Rapid Test – test strip (Biopanda Reagents) to £57,598 per QALY gained for QuikRead Go Strep A test kit (Orion Diagnostica).

TABLE 48 Adult secondary care model: deterministic sensitivity analyses – adverse effect of penicillin

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 15 – halved probability of mild penicillin reaction (rash) to 1%						
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£2034	−0.00169	Dominated
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£618	−0.00046	Dominated
Sensitivity analysis 16 – doubled rates of mild penicillin reaction (rash) to 4%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	−0.00396	Dominated	£1836	0.00107	£1,711,314
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	−0.00396	Dominated	£1636	0.00107	£1,524,891
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£72	0.00804	£8913
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£122	0.00804	£15,136
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£147	0.00804	£18,246
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£97	0.00804	£12,024
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£262	0.00804	£32,557
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£463	0.00599	£77,328
Sensitivity analysis 17 – changed penicillin-induced anaphylaxis from 0.01% (Neuner* et al.*[78]) to 0.64% (Van Howe and Kusnier[79])						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	−0.00396	Dominated	£571	0.01887	£30,270
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	−0.00396	Dominated	£371	0.01887	£19,668
Strep A Rapid Test – cassette (Biopanda Reagents)	£1219	0.00311	£392,342	£45	0.02243	£2024

TABLE 48 Adult secondary care model: deterministic sensitivity analyses – adverse effect of penicillin (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Strep A Rapid Test – test strip (Biopanda Reagents)	£1174	0.00311	£377,852	£0	0.02243	£18
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	–£975	0.02275	Dominant
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	–£925	0.02275	Dominant
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	–£900	0.02275	Dominant
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	–£950	0.02275	Dominant
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	–£785	0.02275	Dominant
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£973	0.0169	£57,598
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	–£618	0.0212	Dominant
Xpert Xpress Strep A (Cepheid)	£1994	0.00395	£504,287	£903	0.02192	£41,202

Note that, of the tests with ICERs in the region of £30,000 per QALY, only the Alere TestPack Plus and QuikRead Go tests used test accuracy data from published peer-reviewed studies. See *Table 15* for more information.

Adults in secondary care: cost of testing in secondary care

In the base case, the cost of confirmatory throat culture following a negative test result was applied to 6 of the 14 tests considered in the analyses [Clearview Exact Strep A cassette (Abbott Laboratories), Clearview Exact Strep A dipstick – test strip (Abbott Laboratories), Strep A Rapid Test – cassette (Biopanda Reagents), Strep A Rapid Test – test strip (Biopanda Reagents), QuikRead Go Strep A test kit (Orion Diagnostica) and Xpert Xpress Strep A (Cepheid)]. Excluding confirmatory throat culture favoured testing. The ICER for Strep A Rapid Test – cassette and test strip supplied by Biopanda Reagents reduced from £392,342 and £377,852 to £26,452 and £11,963 per QALY gained compared with usual care, respectively (*Table 49*).

TABLE 49 Adult secondary care model: deterministic sensitivity analyses – excluding cost of confirmatory throat culture given negative test result

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 20 – assume no swab culture in those with a negative test result						
Strep A Rapid Test – cassette (Biopanda Reagents)	£1219	0.00311	£392,342	£82	0.00311	£26,452
Strep A Rapid Test – test strip (Biopanda Reagents)	£1174	0.00311	£377,852	£37	0.00311	£11,963

Adults in secondary care: utility decrement, group A *Streptococcus* sore throat and related complications

The base-case estimates were sensitive to changes in disutility associated with strep A-related complications (*Table 50*). Decreasing the utility decrement associated with treated infection and the utility decrement for penicillin-induced rash by a half, doubling the decrement associated with untreated infection and doubling the decrement for abscess each favoured usual care, producing ICERs that suggested that usual care dominated testing (see *Table 50* for specific tests) in comparison with the base-case assumptions. Halving the utility decrement for untreated infection and doubling the decrements for treated infection and penicillin-induced rash all favoured testing. The Clearview Exact Strep A cassette (Abbott Laboratories) and Clearview Exact Strep A dipstick – test strip (Abbott Laboratories) were no longer dominated by usual care when the utility decrement associated with penicillin-induced rash was doubled, and the NADAL tests produced ICERs ranging from £21,309 to £44,953 per QALY gained compared with usual care.

TABLE 50 Adult secondary care model: deterministic sensitivity analyses – utility decrement, strep A sore throat and related complications

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 27 – halved utility decrement, untreated infection						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	–0.00396	Dominated	£1957	0.00667	£293,426
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	–0.00396	Dominated	£1757	0.00667	£263,430
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00454	£37,720
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00454	£48,734

TABLE 50 Adult secondary care model: deterministic sensitivity analyses – utility decrement, strep A sore throat and related complications (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00454	£54,242
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00454	£43,228
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£361	0.00454	£79,575
Sensitivity analysis 28 – doubled utility decrement, untreated infection						
Strep A Rapid Test – cassette (Biopanda Reagents)	£1219	0.00311	£392,342	£1219	–0.00022	Dominated
Strep A Rapid Test – test strip (Biopanda Reagents)	£1174	0.00311	£377,852	£1174	–0.00022	Dominated
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00255	£67,224
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00255	£86,852
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00255	£96,668
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00255	£77,040
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£1990	–0.00848	Dominated
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£566	–0.00495	Dominated
Sensitivity analysis 29 – halved utility decrement, treated infection						
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00348	£49,248
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00348	£63,627
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00348	£70,818

continued

TABLE 50 Adult secondary care model: deterministic sensitivity analyses – utility decrement, strep A sore throat and related complications (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00348	£56,439
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£1990	−0.00243	Dominated
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£566	−0.0003	Dominated
Sensitivity analysis 30 – doubled utility decrement, treated infection						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	−0.00396	Dominated	£1957	0.00879	£222,505
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	−0.00396	Dominated	£1757	0.00879	£199,759
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00467	£36,648
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00467	£47,349
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00467	£52,700
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00467	£42,000
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£361	0.00467	£77,313
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£566	0.00567	£99,787
Sensitivity analysis 32 – doubled utility decrement, abscess						
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£1990	−0.00019	Dominated
Sensitivity analysis 35 – halved utility decrement, penicillin-induced rash						
QuikRead Go Strep A test kit (Orion Diagnostica)	£1990	0.00016	£12,700,432	£1990	−0.00169	Dominated
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£566	−0.00046	Dominated

TABLE 50 Adult secondary care model: deterministic sensitivity analyses – utility decrement, strep A sore throat and related complications (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 36 – doubled utility decrement, penicillin-induced rash						
Clearview Exact Strep A cassette (Abbott Laboratories)	£1957	−0.00396	Dominated	£1957	0.00107	£1,823,596
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1757	−0.00396	Dominated	£1757	0.00107	£1,637,173
NADAL Strep A – test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00804	£21,309
NADAL Strep A – cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00804	£27,531
NADAL Strep A plus – cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00804	£30,642
NADAL Strep A plus – test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00804	£24,420
NADAL Strep A scan test – cassette (nal von minden GmbH)	£361	0.00388	£93,211	£361	0.00804	£44,953
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£566	0.00169	£335,358	£566	0.00599	£94,521

Appendix 11 Children's primary care model: exploratory sensitivity analyses

Children's primary care model: Centor threshold for starting antibiotics and testing

In the base-case children's primary care model, a Centor score of ≥ 3 points was used as the cut-off score for starting antibiotic treatment in the usual-care arm and to initiate testing in the intervention arm. Lowering the threshold to a Centor score of ≥ 1 point favoured testing. The ICER for the QuikRead Go Strep A test kit (Orion Diagnostica) and the Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) changed from being dominated in the base case to £2,163,678 and £7,367,395 per QALY gained, respectively, compared with usual care (*Table 51*). Lowering the threshold to a Centor score of ≥ 2 points favoured testing, with the ICER for Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) changing from being dominated in the base case to £5,525,377 per QALY gained compared with usual care. ICERs for the other tests remain unchanged in comparison with base-case ICERs.

Children's primary care model: prevalence of group A *Streptococcus*

Changing the prevalence of strep A infection among children presenting in primary care from 30.2% (base-case value) to 40.1% (upper value reported in studies included in the test accuracy systematic review) had minimal impact on base-case cost-effectiveness results. Changing the prevalence rate to 10% favoured testing but only the ICERs for Clearview Exact Strep A test – cassette (Abbott Laboratories), Clearview Exact Strep A dipstick – test strip (Abbott Laboratories), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) changed from being dominated in the base case to values between £1,319,975 per QALY gained for Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) and £4,635,543 per QALY gained for Clearview Exact Strep A cassette (Abbott Laboratories) compared with usual care (*Table 52*).

TABLE 51 Children's primary care model: deterministic sensitivity analyses – Centor threshold for starting antibiotic therapy

	Base case			Sensitivity analysis		
Test	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 1 – changed Centor threshold for starting antibiotics from ≥ 3 to ≥ 2 points						
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.0008	Dominated	£12,460	0.00226	£5,525,377
Sensitivity analysis 2 – changed Centor threshold for starting antibiotics from ≥ 3 to ≥ 1 points						
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	−0.00318	Dominated	£25,379	0.00344	£7,367,395
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.0008	Dominated	£19,273	0.00891	£2,163,678

TABLE 52 Children's primary care model: deterministic sensitivity analyses – prevalence of strep A

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 5 – changed strep A prevalence from 30.2% to 10% (Neuner et al.[78]*)*						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7588	−0.00714	Dominated	£6088	0.00131	£4,635,543
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£7369	−0.00714	Dominated	£5919	0.00131	£4,507,015
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	−0.00318	Dominated	£6328	0.00247	£2,564,058
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.0008	Dominated	£4707	0.00357	£1,319,975

Children's primary care model: complication rates in treated and untreated group A streptococcal infection

In the base-case analysis, strep A-related complication rates were set to 1.5% for untreated infection and 1.3% for treated strep A infection based on UK primary care data published by Little *et al.*[86] Doubling the complications rate in the treated group to 2.6% favoured testing and changed the ICERs for Clearview Exact Strep A cassette (Abbott Laboratories), Clearview Exact Strep A dipstick – test strip (Abbott Laboratories), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) from being dominated to values between £2,412,772 per QALY gained for Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) and £26,635,474 per QALY gained for Clearview Exact Strep A cassette (Abbott Laboratories) compared with usual care (*Table 53*). Decreasing complications in the untreated group to 0.75% favoured testing and changed the ICER for Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) from being dominated in the base-case analysis to £5,652,302 per QALY gained compared with usual care. The ICERs for all other tests were much lower in comparison with the base-case estimates but remained well above £100,000 per QALY gained in comparison with usual care.

Children's primary care model: side effects of penicillin

Changing the rate of penicillin-induced rash from 0.01% to 0.64%, as reported in Van Howe and Kusnier,[79] favoured testing: the ICERs for Clearview Exact Strep A dipstick – test strip (Abbott Laboratories), Clearview Exact Strep A cassette (Abbott Laboratories), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) changed from being dominated by usual care in the base case, ranging from £264,313 to £404,873 per QALY gained compared with usual care (*Table 54*).

Note that, of the tests with ICERs in the region of £30,000 per QALY, only the Alere TestPack Plus used test accuracy data from published peer-reviewed studies. See *Table 15* for more information.

TABLE 53 Children's primary care model: deterministic sensitivity analyses – complications following strep A infection

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 10 – doubled complications in treated strep A infection to 2.6%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7588	−0.00714	Dominated	£6822	0.00026	£26,635,474
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£7369	−0.00714	Dominated	£6603	0.00026	£25,780,890
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	−0.00318	Dominated	£7348	0.00144	£5,111,532
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.0008	Dominated	£5869	0.00243	£2,412,772
Sensitivity analysis 11 – halved complications in untreated strep A infection to 0.075%						
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.0008	Dominated	£6010	0.00106	£5,652,302

TABLE 54 Children's primary care model: deterministic sensitivity analyses – complications of penicillin

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 16 – doubled rates of mild penicillin reaction (rash) to 4%						
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	−0.00318	Dominated	£7724	0.00113	£6,823,310
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.00080	Dominated	£6100	0.00355	£1,718,859
Sensitivity analysis 17 – changed rates of anaphylaxis from 0.01% (Neuner et al.[78]) to 0.64% (Van Howe and Kusnier[79])						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7588	−0.00714	Dominated	£6211	0.01554	£399,674
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£7369	−0.00714	Dominated	£5992	0.01554	£385,589
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	−0.00318	Dominated	£6638	0.01640	£404,873
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.00080	Dominated	£5005	0.01894	£264,313

Children's primary care model: utility decrement, group A *Streptococcus* sore throat and related complications

As in the adult primary and secondary care models, decreasing the utility decrement associated with untreated strep A by half, doubling the utility treatment for treated strep A and doubling the utility decrement for penicillin-induced rash all favoured testing, and doubling the decrement associated with untreated infection favoured usual care (*Table 55*).

TABLE 55 Children's primary care model: deterministic sensitivity analyses – utility decrements associated with strep A-related complications

	Base case			Sensitivity analysis		
Test	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 27 – halved the utility decrement, untreated strep A						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7588	–0.00714	Dominated	£7588	0.00706	£1,074,366
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£7369	–0.00714	Dominated	£7369	0.00706	£1,043,375
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	–0.00318	Dominated	£7827	0.00569	£1,375,142
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	–0.00080	Dominated	£6204	0.00541	£1,146,652
Sensitivity analysis 28 – doubled utility decrement, untreated strep A						
Strep A Rapid Test – cassette (Biopanda Reagents)	£6715	0.00224	£2,992,743	£6715	–0.00219	Dominated
Strep A Rapid Test – test strip (Biopanda Reagents)	£6665	0.00224	£2,970,792	£6665	–0.00219	Dominated
Sensitivity analysis 30 – doubled utility decrement, treated strep A						
Clearview Exact Strep A cassette (Abbott Laboratories)	£7588	–0.00714	Dominated	£7588	0.00990	£766,212
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£7369	–0.00714	Dominated	£7369	0.00990	£744,109
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	–0.00318	Dominated	£7827	0.00747	£1,048,198
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	–0.00080	Dominated	£6204	0.00665	£932,465

TABLE 55 Children's primary care model: deterministic sensitivity analyses – utility decrements associated with strep A-related complications (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 36 – doubled utility decrement, penicillin-induced rash						
QuikRead Go Strep A test kit (Orion Diagnostica)	£7827	−0.00318	Dominated	£7827	0.00113	£6,914,611
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.0008	Dominated	£6204	0.00355	£1,748,223

Children's primary care model: lower and upper estimates of the accuracy for the clinical score and test

Changing the test accuracy data from the central estimate of test sensitivity and specificity to the lower confidence limit for all tests and the Centor score favoured testing, but the ICER for only Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) changed from being dominated by usual care under the base-case assumption to £13,737,541 per QALY gained compared with usual care (*Table 56*). The upper limits of test sensitivity and specificity favoured testing (results not presented) but none of the ICERs changed substantially to suggest different interpretation of base-case cost-effectiveness results.

TABLE 56 Children's primary care model: deterministic sensitivity analyses – lower limits of CIs for test accuracy data

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 39 – lower confidence limits of test accuracy						
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£6204	−0.0008	Dominated	£6987	0.00051	£13,737,541

Appendix 12 Children's secondary care model: exploratory sensitivity analyses

Children's secondary care model: Centor threshold for starting antibiotics and testing

In the base-case model for children treated in secondary care, a threshold of a Centor score of ≥ 3 points plus clinical assessment was used as the basis for immediate antibiotic treatment in the usual-care arm and to initiate testing in the intervention arm. Changing this threshold to a Centor score of ≥ 2 points had minimal impact on the base-case cost-effectiveness of all tests included in the analysis [except the Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)]. Using a threshold of a Centor score of ≥ 1 point favoured testing and changed the ICERs for the Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) and the QuikRead Go Strep A test kit (Orion Diagnostica) from being dominated in the base case to £205,449 per QALY gained and £2,303,715 per QALY gained compared with usual care, respectively (*Table 57*).

Children's secondary care model: prevalence of group A *Streptococcus*

Changing the prevalence of strep A infection among children presenting in secondary care from 30.2%[24] to 40.1%[48] (upper value reported in studies included in the test accuracy systematic review) had minimal

TABLE 57 Children's secondary care model: deterministic sensitivity analyses – Centor threshold for starting antibiotics and testing

	Base case			Sensitivity analysis		
Test	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 1 – changed Centor threshold for starting antibiotics from ≥ 3 (base case) to ≥ 2 points						
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£371	0.00879	£42,226
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£482	0.00879	£54,800
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£537	0.00879	£61,086
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£426	0.00879	£48,513
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	£791	0.00879	£90,007
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£1241	0.00226	£550,135

continued

TABLE 57 Children's secondary care model: deterministic sensitivity analyses – Centor threshold for starting antibiotics and testing (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 2 – changed Centor threshold for starting antibiotics from ≥ 3 (base case) to ≥ 1 points						
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£495	0.01670	£29,604
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£666	0.01670	£39,891
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£752	0.01670	£45,035
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£580	0.01670	£34,748
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	£1148	0.01670	£68,697
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	–0.00318	Dominated	£7936	0.00344	£2,303,715
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£1830	0.00891	£205,449

impact on the base-case ICERs in the children's secondary care model. In contrast (*Table 58*), a lower prevalence of disease at 10% was more favourable to testing, with ICERs ranging from £20,575 per QALY gained for NADAL Strep A – test strip (nal von minden GmbH) to £1,374,151 per QALY gained for the Clearview Exact Strep A cassette (Abbott Laboratories) compared with usual care. ICERs for all other tests did not change substantially to change the direction of the base-case cost-effectiveness estimates.

Children's secondary care model: complication rates

Halving complications in the treated group to 0.65%, the ICER was favourable to testing for the Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) in comparison with ICERs produced under base-case assumptions. Doubling the complications rate in the treated group to 2.6% favoured testing; the ICER for the Clearview Exact Strep A dipstick – test strip (Abbott Laboratories), Clearview Exact Strep A cassette (Abbott Laboratories), Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) and QuikRead Go Strep A test kit (Orion Diagnostica) changed from being dominated by usual care to between £1,247,882 [Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)] and £4,949,827 [Clearview Exact Strep A cassette (Abbott Laboratories)] per QALY gained compared with usual care (*Table 59*). ICERs for all other tests were much lower in comparison with the base-case estimates but still remained well above £100,000 per QALY gained in comparison with usual care.

TABLE 58 Children's secondary care model: deterministic sensitivity analyses – prevalence of strep A infection among children presenting in secondary care

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 5 – changed strep A prevalence from 22.6% to 10%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£2034	−0.00714	Dominated	£1805	0.00131	£1,374,151
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1815	−0.00714	Dominated	£1636	0.00131	£1,245,623
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£100	0.00488	£20,575
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£143	0.00488	£29,227
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£164	0.00488	£33,553
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£121	0.00488	£24,901
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	£261	0.00488	£53,453
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	−0.00318	Dominated	£2045	0.00247	£828,590
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	−0.0008	Dominated	£424	0.00357	£118,942

TABLE 59 Children's secondary care model: deterministic sensitivity analyses – complications of strep A infection

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 10 – doubled complications in treated infection to 2.6%						
Clearview Exact Strep A cassette (Abbott Laboratories)	£2034	−0.00714	Dominated	£1268	0.00026	£4,949,827
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1815	−0.00714	Dominated	£1049	0.00026	£4,095,204

continued

TABLE 59 Children's secondary care model: deterministic sensitivity analyses – complications of strep A infection (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£165	0.00374	£44,246
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£220	0.00374	£58,899
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£247	0.00374	£66,225
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£193	0.00374	£51,574
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	£373	0.00374	£99,924
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	–0.00318	Dominated	£1794	0.00144	£1,247,882
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£314	0.00243	£129,172
Sensitivity analysis 11 – halved complications in untreated infection to 0.75%						
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£456	0.00106	£428,791

Children's secondary care model: adverse effects of penicillin

Cost-effectiveness estimates were most sensitive to the adverse effects of penicillin. Halving the mild/uncomplicated side effects of penicillin (rash) to 1.0% favoured usual care (results not shown here), and doubling it favoured testing (*Table 60*). Changing the rate of penicillin-induced anaphylaxis from 0.01% to 0.64% favoured testing and generated ICERs with the Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) and the NADAL tests all dominating usual care. The Clearview Exact Strep A dipstick – test strip and cassette supplied by Abbott Laboratories produced ICERs of £28,181 and £42,266 per QALY gained, and the Strep A Rapid Test – test strip and cassette supplied by Biopanda Reagents produced £1643 and £4105 per QALY gained compared with usual care (see *Table 60*). The Xpert Xpress Strep A (Cepheid) and QuikRead Go Strep A test kit (Orion Diagnostica) produced ICERs of £51,637 and £66,111 per QALY gained, respectively. ICERs for the Alere i Strep A 2 (Abbott Laboratories) and cobas Liat Strep A Assay (Roche Diagnostics) remained above £100,000 per QALY gained compared with usual care (not displayed in *Table 60*).

Note that, of the tests with ICERs in the region of £30,000 per QALY, only the Alere TestPack Plus used test accuracy data from published peer-reviewed studies. See *Table 15* for more information.

TABLE 60 Children's secondary care model: deterministic sensitivity analyses – adverse effects of penicillin

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 16 – doubled rates of mild penicillin reaction (rash) to 4%						
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£123	0.00705	£17,378
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£177	0.00705	£25,134
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£205	0.00705	£29,013
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£150	0.00705	£21,256
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	£331	0.00705	£46,855
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	−0.00318	Dominated	£2169	0.00113	£1,916,392
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	−0.0008	Dominated	£545	0.00355	£153,598
Sensitivity analysis 17 – changed penicillin-induced anaphylaxis from 0.01% (Neuner* et al.*[78]) to 0.64% (Van Howe and Kusnier[79])						
Clearview Exact Strep A cassette (Abbott Laboratories)	£2034	−0.00714	Dominated	£657	0.01554	£42,266
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1815	−0.00714	Dominated	£438	0.01554	£28,181
Strep A Rapid Test – cassette (Biopanda Reagents)	£1160	0.00224	£517,066	£82	0.02000	£4105
Strep A Rapid Test – test strip (Biopanda Reagents)	£1111	0.00224	£495,115	£33	0.02000	£1643
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	−£828	0.02043	Dominant
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	−£773	0.02043	Dominant
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	−£746	0.02043	Dominant

continued

TABLE 60 Children's secondary care model: deterministic sensitivity analyses – adverse effects of penicillin (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	–£801	0.02043	Dominant
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	–£620	0.02043	Dominant
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	–0.00318	Dominated	£1084	0.0164	£66,111
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	–£549	0.01894	Dominant
Xpert Xpress Strep A (Cepheid)	£2006	0.00349	£574,900	£1019	0.01974	£51,637

Children's secondary care model: cost of testing in secondary care

Excluding confirmatory throat culture costs following a negative test result favoured testing and generated ICERs ranging from £29,702 per QALY gained for Strep A Rapid Test – test strip (Biopanda Reagents) to £51,653 per QALY gained for the Strep A Rapid Test – cassette (Biopanda Reagents) compared with usual care (*Table 61*).

Children's secondary care model: utility decrement and group A *Streptococcus*-related complications

The base-case estimates were sensitive to changes in disutility associated with strep A-related complications (*Table 62*). Scenarios that favoured testing include decreasing the utility decrement of untreated infection by half, doubling the decrement of treated infection and doubling the decrement

TABLE 61 Children's secondary care model: deterministic sensitivity analyses – excluding costs of confirmatory culture given negative test result

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 20 – assume no swab culture in those with a negative test result						
Strep A Rapid Test – cassette (Biopanda Reagents)	£1160	0.00224	£517,066	£116	0.00224	£51,653
Strep A Rapid Test-test strip (Biopanda Reagents)	£1111	0.00224	£495,115	£67	0.00224	£29,702

TABLE 62 Children's secondary care model: deterministic sensitivity analyses – utility decrement, strep A sore throat and related complications

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 27 – halved utility decrement, untreated infection						
Clearview Exact Strep A cassette (Abbott Laboratories)	£2034	–0.00714	Dominated	£2034	0.00706	£287,940
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1815	–0.00714	Dominated	£1815	0.00706	£256,947
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£213	0.00416	£51,228
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£268	0.00416	£64,383
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£295	0.00416	£70,959
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£240	0.00416	£57,804
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	–0.00318	Dominated	£2273	0.00569	£399,281
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£649	0.00541	£120,004
Sensitivity analysis 28 – doubled utility decrement, untreated infection						
Strep A Rapid Test – cassette (Biopanda Reagents)	£1160	0.00224	£517,066	£1160	–0.00219	Dominated
Strep A Rapid Test – test strip (Biopanda Reagents)	£1111	0.00224	£495,115	£1111	–0.00219	Dominated
Sensitivity analysis 30 – doubled utility decrement, treated infection						
Clearview Exact Strep A cassette (Abbott Laboratories)	£2034	–0.00714	Dominated	£2034	0.00990	£205,352
Clearview Exact Strep A dipstick – test strip (Abbott Laboratories)	£1815	–0.00714	Dominated	£1815	0.00990	£183,248
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£213	0.00434	£49,131
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£268	0.00434	£61,748

continued

TABLE 62 Children's secondary care model: deterministic sensitivity analyses – utility decrement, strep A sore throat and related complications (*continued*)

Test	Base case			Sensitivity analysis		
	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£295	0.00434	£68,055
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£240	0.00434	£55,438
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	£421	0.00434	£97,068
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	–0.00318	Dominated	£2273	0.00747	£304,351
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£649	0.00665	£97,588
Sensitivity analysis 36 – doubled utility decrement, penicillin-induced rash						
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£213	0.00705	£30,212
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£268	0.00705	£37,970
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£295	0.00705	£41,848
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£240	0.00705	£34,090
NADAL Strep A scan test – cassette (nal von minden GmbH)	£421	0.00327	£128,662	£421	0.00705	£59,689
QuikRead Go Strep A test kit (Orion Diagnostica)	£2273	–0.00318	Dominated	£2273	0.00113	£2,007,701
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£649	0.00355	£182,962

associated with mild penicillin reaction. The ICER for the Clearview Exact Strep A cassette and test strip supplied by Abbott Laboratories were no longer dominated by usual care, and ICERs for NADAL's tests remained under £100,000 per QALY gained compared with usual care. In contrast, doubling the utility decrement of untreated infection was less favourable to testing and resulted in Strep A Rapid Test – cassette (Biopanda Reagents) and Strep A Rapid Test – test strip (Biopanda Reagents) being dominated by usual care (see *Table 62*).

Children's secondary care model: lower and upper estimates of the accuracy for the clinical score and test

Changing the test accuracy data from the central estimate of test sensitivity and specificity to the lower confidence limit for all tests and the Centor score favoured testing, but only the ICER for Alere TestPack +Plus Strep A – cassette (Abbott Laboratories) changed from being dominated by usual care under base-case assumption to £1,356,265 per QALY gained compared with usual care, whereas ICERs for NADAL's tests remained under £100,000 per QALY gained compared with usual care (*Table 63*). The upper limits of test sensitivity and specificity favoured testing (results not presented) but none of the ICERs changed substantially to suggest a different interpretation of base-case cost-effectiveness results.

TABLE 63 Children's secondary care model: deterministic sensitivity analyses – lower limits of CIs for test accuracy data

	Base case			Sensitivity analysis		
Test	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER	Incremental costs per 1000 individuals	Incremental QALYs per 1000 individuals	ICER
Sensitivity analysis 39 – lower confidence limits of test accuracy						
NADAL Strep A – test strip (nal von minden GmbH)	£213	0.00327	£65,122	£208	0.00378	£54,933
NADAL Strep A – cassette (nal von minden GmbH)	£268	0.00327	£81,845	£270	0.00378	£71,352
NADAL Strep A plus – cassette (nal von minden GmbH)	£295	0.00327	£90,205	£301	0.00378	£79,562
NADAL Strep A plus – test strip (nal von minden GmbH)	£240	0.00327	£73,482	£239	0.00378	£63,143
Alere TestPack +Plus Strep A – cassette (Abbott Laboratories)	£649	–0.0008	Dominated	£690	0.00051	£1,356,265

Appendix 13 Additional sensitivity analyses

TABLE 64 List of additional sensitivity analyses

Sensitivity analysis	Description of sensitivity analysis	Updated input parameter
0	Base case	
1	Changed Centor threshold score for starting antibiotics from ≥ 3 (base case) to ≥ 2 points	2
2	Changed Centor threshold score for starting antibiotics from ≥ 3 (base case) to ≥ 1 points	1
3	**Changed time horizon to 14 days**	**14**
4	Changed strep A prevalence (adults) from 22.6% to 35.9% (upper value reported in studies included in the test accuracy systematic review)	0.359
5	Changed strep A prevalence (adults) from 22.6% to 10% (Neuner *et al.*[78])	0.1
6	Delayed prescription rate set to 27.3% in both arms (RADT group, Little *et al.*[6])	0.273
7	Delayed prescription rate set to 51% in both arms (clinical score group, Little *et al.*[6])	0.51
8	Doubled proportion who use delayed antibiotics to 92%	0.92
9	Halved probability of strep A complications when given antibiotics from 0.013 (Little *et al.*[6]) to 0.0065 (analyst assumption)	0.0065
10	Doubled probability of strep A complications when given antibiotics from 0.013 (Little *et al.*[6]) to 0.026 (analyst assumption)	0.026
11	Halved probability of strep A complications when given no antibiotics from 0.015 (Little *et al.*[6]) to 0.0075 (analyst assumption)	0.0075
12	Doubled probability of strep A complications when given no antibiotics from 0.015 (Little *et al.*[6]) to 0.03 (analyst assumption)	0.03
13	Halved probability of rheumatic fever to 0.00005	0.00005
14	Increased probability of rheumatic fever 10-fold to 0.001	0.001
15	Halved mild penicillin reaction (rash) to 0.01	0.01
16	Doubled mild penicillin reaction (rash) to 0.04	0.04
17	Changed probability of anaphylaxis from 0.0001 (Neuner *et al.*[78]) to 0.0064 (Van Howe and Kusnier[79])	0.0064
18	Changed cost of antibiotics from £0.74 (BNF,[91] 15 capsules of amoxicillin 500 mg) to £6.11 (NG51 costing report[118])	6.11
19	Assume that patient is seen by practice nurse (£62/hour, PSSRU,[90] section 10.1) instead of doctor	1.03
20	Assume no swab culture in those with a negative test result	0
21	Double the cost of alternative antibiotic in those with penicillin-induced rash to £20	20
22	Assume testing within standard GP time	Yes
23	Doubled cost of anaphylaxis to £3489.28	£3489.28
24	Doubled cost of abscess to £3142.56	£3142.56
25	Doubled cost of acute rheumatic fever to £3544.88	£3544.88
26	Changed baseline utility from 0.863 (UK norm) to 0.6305 (PRISM study, table 17[6])	0.6305

continued

TABLE 64 List of additional sensitivity analyses (*continued*)

Sensitivity analysis	Description of sensitivity analysis	Updated input parameter
27	Halved utility decrement, untreated strep A	0.125
28	Doubled utility decrement, untreated strep A	0.5
29	Halved utility decrement, treated strep A	0.075
30	Doubled utility decrement, treated strep A	0.3
31	Halved utility decrement, strep A-related abscess	2.5
32	Doubled utility decrement, strep A-related abscess	10
33	Halved utility decrement, acute rheumatic fever	38.25
34	Doubled utility decrement, acute rheumatic fever	153
35	Halved utility decrement, penicillin-induced rash	0.3125
36	Doubled utility decrement, penicillin-induced rash	1.25
37	Halved utility decrement, strep A-related sepsis	4.5
38	Doubled utility decrement, strep A-related sepsis	18
39	Lower confidence limits of test accuracy	
40	Upper confidence limits of test accuracy	

BNF, *British National Formulary*; PSSRU, Personal Social Services Research Unit.

Note

Bold and shaded rows indicate the sensitivity analysis number, description of sensitivity analysis, location in the model Microsoft Excel workbook where the changes were made and the updated model input used in the sensitivity analysis.

Appendix 14 Summary of manufacturers' information

Biopanda Reagents

1. Checklist of confidential information.
2. Product insert: Strep A Rapid Test RAPG-STRA-001.
3. Declaration of conformity DOCSTRA1826.
4. Response to request for information.

Cepheid

1. Package insert: Xpert Xpress Strep A XPRSTREPA-CE-10.
2. CE declaration of conformity.
3. The GeneXpert System. CE-IVD test menu 2.
4. The GeneXpert System. CE-IVD test menu.
5. Ferrieri *et al.*[85]
6. Matthys *et al.*[119]
7. Response to request for information.
8. Xpert Xpress Strep A brochure CEIVD 3106-01.A.
9. Xpert Xpress Strep A datasheet CEIVD 3105-01.

nal von minden GmbH

1. Gazzano *et al.*[120]

NADAL Strep A

1. EC-declaration of conformity for product number 221002A – signed 30 January 2017.
2. EC-declaration of conformity for product number 221002A – signed 9 February 2017.
3. EC-declaration of conformity for product number 222008 – signed 28 July 2017.
4. Instructions for use for NADAL Strep A Test (test strip), reference 221001A, version 2.2, 11 August 2017.
5. Instructions for use for NADAL Strep A Test (test cassette), reference 222001A, version 2.3, 24 October 2017.
6. Checklist of confidential information. For test strip.
7. Checklist of confidential information. For cassette.
8. Response to request for information NADAL Strep A cassette.
9. Response to request for information NADAL Strep A test strip.

NADAL Strep A plus

1. EC-declaration of conformity. Product number 221050N-50.
2. Instructions for use for NADAL Strep A plus Test (test strip) 221050N-50.
3. Instructions for use for NADAL Strep A plus Test (test cassette) 222007.
4. Instructions for use for NADAL Strep A plus Test (test cassette) 222008.
5. Checklist of confidential information. For test strip.
6. Checklist of confidential information. For test cassette.
7. Response to request for information NADAL Strep A+ cassette.
8. Response to request for information NADAL Strep A+ test strip.

NADAL Strep A Scan

1. EC-declaration of conformity. Product number 222049NBUL-20.
2. Instructions for use for NADAL Strep A scan test (test cassette) 222049NBUL-20.
3. Checklist of confidential information. For NADAL Strep A scan (cassette).
4. Response to request for information NADAL Strep A scan (cassette).

Orion Diagnostica

1. Shallcross and Davies.[121]
2. Checklist of confidential information. 10122018.
3. Clinical impact of rapid POC test for acute sore throat poster ECCMID 2016. URL: www.oriondiagnostica.com/globalassets/documents-and-materials/quikread-go/quikread-go-strep-a/9031_clinical_impact_of_rapid_poc_tests_for_accute_sore_throat_eccmid_2016_a3_web.pdf (accessed 17 April 2019).
4. Response to request for information.
5. Declaration of conformity for QuikRead Go Strep A System and QuikRead Go Strep A cat. no 135883.
6. Instructions for use QuikRead Go Strep A. 136262-3.
7. Poster ESPID 2013.
8. QuikRead Go Strep A – an evaluation of performance in comparison with Alere TestPack+Plus with OBC, by Oulun Työterveys laboratory.
9. Evaluation of QuikRead Go Strep A test regarding the detection level of *Streptococcus pyogenes*, by Pia Karlsson at Microbiology laboratory of Medicinsk Diagnostik, Jönköping, Sweden.
10. Stefaniuk *et al.*[52]
11. The report from Scandinavian evaluation of laboratory equipment for primary health care (SKUP) on QuikRead Go Strep A.

Roche Diagnostics

1. Declaration of conformity DOC-2017-38.
2. cobas Strep A – nucleic acid test for use on the cobas Liat system – package insert.
3. Response to request for information.
4. Checklist of confidential information.

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